



(18E1) 18E1

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Hewick, et al.

Serial No. : 07/800,364

Examiner: K. Furman

Filed : November 26, 1991

Art Unit: 1814

For : DNA ENCODING AND METHODS
FOR PRODUCING BMP-8 PROTEINS

RECEIVED

DEC 11 1995

GROUP 1800

Honorable Commissioner of Patents
and Trademarks
BOX RECONSTRUCTION
Washington, D.C. 20231

STATEMENT

In response to the request of September 20, 1995, attached is a copy of the Office Actions and Amendment papers. This affirms that to the best of my knowledge and belief, the attached list of papers (Appendix A) constitutes our records of the above-identified patent application insofar as it concerns the Patent and Trademark Office.

CERTIFICATE OF MAILING

Respectfully submitted,

Date of Deposit November 15, 1995
I hereby certify that this correspondence is being deposited with the
U.S. Postal Service under 37 CFR §1.8 as first class mail in an
envelope addressed to Honorable Commissioner of Patents and
Trademarks, BOX RECONSTRUCTION, Washington, D.C. 20231,
on the date of deposit as indicated above.

Diana Gentile

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Attorney of Record

LEGAL AFFAIRS
GENETICS INSTITUTE, INC.
87 CambridgePark Drive
Cambridge, Massachusetts 02140
Telephone: (617) 498-8622
Facsimile: (617) 876-5851
Dated: November 15, 1995

APPENDIX A

1. Correspondence from Patent and Trademark Office requesting application papers for reconstruction dated September 20, 1995.
2. Correspondence from Patent and Trademark Office dated September 20, 1995, advising that the Amendment filed July 31, 1995, has been considered.
3. Letter to the Patent and Trademark Office dated September 8, 1995, enclosing a certified copy of PCT/US91/03388.
4. Submission of Issue Fee to Patent and Trademark Office dated August 11, 1995.
5. Petition Under 37 CFR §1.84(b) dated July 26, 1995, and Figure 1.
6. Amendment under 37 CFR §1.312 and Response to Requirement for Substitute Declaration dated July 26, 1995.
7. Notice of Allowability, Notice of Allowance and Issue Fee Due dated May 15, 1995.
8. Amendment dated January 30, 1995.
9. Advisory Action dated November 8, 1994.
10. Office Action dated April 7, 1994.
11. Communication from Patent and Trademark Office notifying withdrawal of abandonment dated February 9, 1994.
12. Amendment, Notice of Appeal, Response to Notice and Submission of Formal Drawings w/Form 948, Sequence Listing, Statement under §1.825(b) and (a) dated October 5, 1994.
13. Letter with enclosures to Patent and Trademark Office requesting Notice of Abandonment be withdrawn dated January 13, 1994.
14. Notice of Abandonment dated September 14, 1993.
15. Amendment, Declaration of Deposit Requirements with enclosures, Information Disclosure Statement dated August 4, 1993.
16. Office Action dated February 5, 1993.
17. Preliminary Amendment, Statement pursuant to 37 CFR §1.825(a), Statement pursuant to 37 CFR §1.821(f), and Sequence Listing dated November 11, 1992.

APPENDIX A (continued)

18. Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures dated August 12, 1992.
19. Recorded Assignment dated January 27, 1992.
20. Filing Receipt received March 15, 1992.
21. Response to Notice to File Missing Parts of Application under 37 CFR §1.53(d), Declaration and Power of Attorney dated January 24, 1992.
22. Notice to File Missing Parts of Application dated January 6, 1992.



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

(1)

Date: September 20, 1995

Legal Affairs Dept.
Genetics Institute, Inc.
87 Cambridgepark Dr.
Cambridge, MA 02140

App. Serial No: 07/800,364

Patent No.:

Inventor(s): Hewick et al.

Filed: 11/26/91

Title of Invention: **DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS**

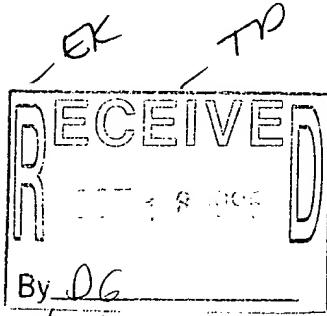
We are unable to locate the file identified above. An exhaustive search has been made throughout the Patent and Trademark Office, but the file cannot be found. There fore, we would like to replace the lost file with an authentic duplicate.

We have obtained a copy of the original application papers from our security film and would appreciate the loan of your official record, or a legible copy thereof, of the Office Actions and Amendment Papers in order to complete this file. Please include a list of the papers and a sworn statement that the papers listed constitute your record of this application insofar as it concerns the Patent and Trademark Office.

Please direct your reply to:

U.S. Patent and Trademark Office
Box Reconstruction
Washington, D.C. 20231
(703)308-9726

Dorothy Smith
Certification Division



11/20/95 respond to Patent office Request

GI 5182A



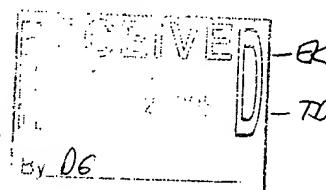
UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

(2)

| | | | | |
|---------------|----------|-------------|-------------------------|------------------------|
| SERIAL NUMBER | 11/26/91 | FILING DATE | FIRST NAME OF APPLICANT | LAST NAME OF APPLICANT |
| 07/800,364 | | | HENICK | P 51820 |
| | | | FURNISH | EXAMINER |
| | | 18M2/0920 | | |
| | | | ART. UNIT | PAPER NUMBER |
| | | | 1814 | |
| | | | DATE MAILED/RECD | |
| | | | 7/31/95 | |

A. The petition filed _____ under 37 CFR 1.312(b) is granted.
The paper has been forwarded to the examiner for consideration on the merits.



B. The amendment filed 7/31/95 under 37 CFR 1.312 has been
considered, and has been:

1. entered
2. entered as directed to matters of form not affecting the scope of the invention (0.3311).
3. disapproved. A report appears below.
4. entered in part. A report appears below.

Report:

ROBERT A. WAX
SUPERVISORY PATENT EXAMINER
GROUP 180

PLEASE FURNISH YOUR ZIP CODE IN ALL CORRESPONDENCE

(3)

CERTIFICATE OF MAILING

Date of Deposit

September 13, 1995

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GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rodney M. Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

For : DNA ENCODING AND METHODS
FOR PRODUCING BMP-8 PROTEINS

September 8, 1995

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

LETTER

Enclosed is a certified copy of PCT/US91/03388.

Respectfully submitted,



Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617) 498-8622

Legal Affairs
Genetics Institute, Inc.
87 Cambridge Park Drive
Cambridge, MA 02140

FILING DATE

15 MAY 1991

PCT/US 91/03388

| SE | NUMBER | FILING DATE | CLASS | SUBCLASS | GROUP ART UNIT | EXAMINER |
|----|-----------|-------------|-------|----------|----------------|----------|
| | 511/03388 | 15 MAY 1991 | | | ISA/ EP | |

APPLICANT'S

GENETICS INSTITUTE, INC.

UNITED STATES OF AMERICA

525,357

16 MAY 1990

UNITED STATES OF AMERICA

641,204

15 JANUARY 1991

| Foreign priority claimed 35 USC 119 conditions met | <input type="checkbox"/> yes <input type="checkbox"/> no | <input type="checkbox"/> yes <input type="checkbox"/> no | AS FILED | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEP. CLAIMS | FILING FEE RECEIVED | ATTORNEY'S DOCKET NO. |
|---|--|--|----------|------------------|-----------------|--------------|---------------|---------------------|-----------------------|
| | | | → | 025 | 1 | 16 | 8 | | GI 5132X-? |

ADDRESS

ELLEN J. KAPINOS
 LEGAL AFFAIRS
 GENETICS INSTITUTE, INC.
 87 CAMBRIDGE PARK DRIVE
 CAMBRIDGE, MASSACHUSETTS 02140

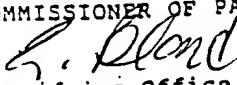
TITLE

BONE AND CARTILAGE INDUCTIVE PROTEINS

This is to certify that annexed hereto is a true copy of the above-identified International application as originally filed and any corrections thereto from the records of the United States Patent and Trademark Office acting as a Receiving Office under the Patent Cooperation Treaty.

By authority of the

COMMISSIONER OF PATENTS AND TRADEMARKS


 Certifying Office

Date AUG 24 1995



Cambridge, MA 02140
87 Cambridge Park Drive
Legal Affairs
Inc.

PATENT

Serial No. 07/600,364 Doc. No. 615152A Atty/Sec EK/DL Date Sept 13, 1995

Inventor Rodney M. Hewick et al

Title DNA Encoding and Methods for Producing BMP-5 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

pp. Spec., claims (1-), Abstract pp. Preliminary Amendment
 pp. Sequence ID Listing/Computer Diskette pp. Amendment/Response
 pp. Statement re Sequence ID Listing pp. Declaration/Exhibits
 pp. Declaration/Power of Attorney pp. Transmittal Letter (triplicate)
 shts. Informal/Formal Drawings 42 15 pp. Appeal Brief (triplicate)
 pp. Assignment & Fee Issue Fee
 pp. Extension of Time & Fee (duplicate) Notice of Appeal & Fee
 pp. Information Disclosure Statement & Fee *copy of PCT/US91/03358*
with PTO-1449 and references



The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Respectfully,
Genetics Institute, Inc.

PATENT

Express Mail Label No. _____

Serial No. 07/600,364 Dc

Inventor Rodney M. Hewick et al

Title DNA Encoding and Methods for Producing BMP-5 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

pp. Spec., claims (1-), Abstract pp. Preliminary Amendment
 pp. Sequence ID Listing/Computer Diskette pp. Amendment/Response
 pp. Statement re Sequence ID Listing pp. Declaration/Exhibits
 pp. Declaration/Power of Attorney pp. Transmittal Letter (triplicate)
 shts. Informal/Formal Drawings 42 15 pp. Appeal Brief (triplicate)
 pp. Assignment & Fee Issue Fee
 pp. Extension of Time & Fee (duplicate) Notice of Appeal & Fee
 pp. Information Disclosure Statement & Fee *copy of PCT/US91/03358*
with PTO-1449 and references

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Genetics Institute, Inc.

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4

CERTIFICATE OF EXPRESS MAILING

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Date of Deposit August 11, 1995

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Diana Gentile

GI-5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit: 1814 Examiner: K. Furman

Applicant: Rodney M. Hewick et al. Issue Batch: L54

Serial No.: 07/800,364 Date of Allowance: May 15, 1995

Filed: November 26, 1991

For: DNA ENCODING AND METHODS
FOR PRODUCING BMP-8 PROTEINS

August 11, 1995

Hon. Commissioner of Patents

and Trademarks

BOX ISSUE FEE

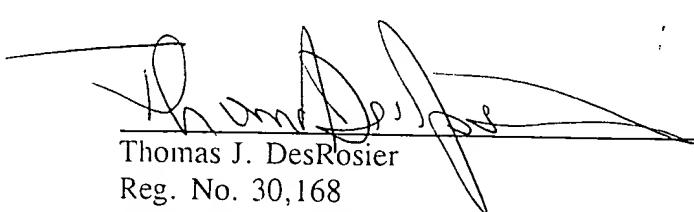
Washington, D.C. 20231

SUBMISSION OF ISSUE FEE

Applicants submit herewith authorization and appropriate forms PTOL-85b and PTOL-85c for charging the Issue Fee and any other fees that may be due in this case to Deposit Account No. 07-1060.

As indicated in the Notice, the deadline for submitting the Issue Fee is August 15, 1995. This response should therefore be deemed timely filed.

Respectfully submitted,


Thomas J. DesRosier
Reg. No. 30,168
Attorney for Applicants

LEGAL AFFAIRS
GENETICS INSTITUTE, INC.
87 Cambridge Park Drive
Cambridge, MA 02140
Telephone: (617) 498-8622
Telefax: (617) 876-5851

PART B—ISSUE FEE TRANSMITTAL

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to addressee entered in Block 1 unless you direct otherwise, by: (a) specifying a new correspondence address in Block 3 below; or (b) providing the PTO with a separate "FEE ADDRESS" for maintenance fee notifications with the payment of Issue Fee or thereafter. See reverse for Certificate of Mailing.

| | | | |
|--|--|--|--|
| 1. CORRESPONDENCE ADDRESS | | 2. INVENTOR(S) ADDRESS CHANGE (Complete only if there is a change) | |
| <p align="right">18M2/0515</p> <p>LEGAL AFFAIRS DEPT. GENETICS INSTITUTE, INC. 87 CAMBRIDGE PARK DR. CAMBRIDGE, MA 02140</p> | | INVENTOR'S NAME | |
| | | Street Address | |
| | | City, State and ZIP Code | |
| | | CO-INVENTOR'S NAME | |
| | | Street Address | |
| | | City, State and ZIP Code | |
| <input type="checkbox"/> Check if additional changes are on reverse side | | | |

| SERIES CODE/SERIAL NO. | FILING DATE | TOTAL CLAIMS | EXAMINER AND GROUP ART UNIT | DATE MAILED |
|------------------------|-------------|--------------|-----------------------------|---------------|
| 97/000,364 | 11/26/91 | 004 | FURMAN, K | 1014 08/15/95 |
| First Named Applicant | HEWICK, | | RODNEY M. | |

TITLE OF INVENTION

DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS
(AS AMENDED)

| | ATTY'S DOCKET NO. | CLASS-SUBCLASS | BATCH NO. | APPLN. TYPE | SMALL ENTITY | FEES DUE | DATE DUE |
|---|-------------------|----------------|-----------|-------------|--------------|-----------|----------|
| 1 | 5192A | 435-240-200 | L54 | UTILITY | NO | \$1210.00 | 08/15/95 |

3. Correspondence address change (Complete only if there is a change)

4. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.

1 Ellen J. Kapinos

2 Thomas J. DesRosier

3 _____

DO NOT USE THIS SPACE

5. ASSIGNMENT DATA TO BE PRINTED ON THE PATENT (print or type)

(1) NAME OF ASSIGNEE:

Genetics Institute, Inc.

(2) ADDRESS: (CITY & STATE OR COUNTRY)

Cambridge, Massachusetts 02140

U.S.A.

6a. The following fees are enclosed:

Issue Fee Advance Order - # of Copies 10

6b. The following fees should be charged to:

DEPOSIT ACCOUNT NUMBER 07-1060

(ENCLOSE PART C)

Issue Fee Advance Order - # of Copies _____

Any Deficiencies in Enclosed Fees

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Authorized Signature)

(Date)

Thomas J. DesRosier

8/11/95

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

Vice President and Chief Patent Counsel

1. MAILING INVOICE WITH FEE CERTIFICATE OF MAILING ON REVERSE

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

Box ISSUE FEE
Commissioner of Patents and Trademarks
Washington, D.C. 20231

on August 11, 1995
(Date)

Diana Gentile
(Name of person making deposit)
Diana Gentile
(Signature)

August 11, 1995
(Date)

Note: If this certificate of mailing is used, it can only be used to transmit the Issue Fee. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Office of Information Systems, Patent and Trademark Office, Washington, D.C. 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget, (Project 0651-0033), Washington, D.C. 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner of Patents and Trademarks, Box Issue Fee, Washington, DC 20231.

PART C—CHARGE TO DEPOSIT ACCOUNT

1. CORRESPONDENCE ADDRESS

18962, 05115

LEGAL AFFAIRS DEPT.
GENETICS INSTITUTE, INC.
87 CAMBRIDGE PARK DR.
CAMBRIDGE, MA 02140

| SERIES CODE/SERIAL NO. | FILING DATE | TOTAL CLAIMS | EXAMINER AND GROUP ART UNIT | DATE MAILED |
|--------------------------|-------------|--------------|-----------------------------|-------------|
| First Named Applicant | 10/10/95 | 11/27/95 | 1004 | PTO/PLA, M |

**TITLE OF
INVENTION**

GENETIC ENGINEERING AND ITS APPLICATIONS FOR PRODUCTION OF POLY(ADENYLIC ACID) ANALOGUE

| ATTY'S DOCKET NO. | CLASS-SUBCLASS | BATCH NO. | APPLN. TYPE | SMALL ENTITY | FEES DUE | DATE DUE |
|-------------------|----------------|-----------|-------------|--------------|----------|----------|
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DO NOT USE THIS SPACE

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 Issue Fee Advance Order - # of Copies _____

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DEPOSIT ACCOUNT NUMBER 07-1060

Issue Fee Advance Order - # of Copies _____
 Any Deficiencies in Enclosed Fees _____

The COMMISSIONER OF PATENTS AND TRADEMARKS is
requested to apply the Issue Fee to the application identified above.

(Authorized Signature)

Thomas J. Desrosier

8/11/95

NOTE: The Issue Fee will not be accepted from anyone other than the
applicant; a registered attorney or agent; or the assignee or other party
in interest as shown by the records of the Patent and Trademark Office.

Vice President and Chief Patent Counsel

PATENT

Serial No. 07/800,364 Doc. No. GT 51824 Atty/Sec. EK/06 Date 8/11/95
Inventor Rodney M. Henick et al.
Title PAV Encoding and Methods for Producing BMP-8

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

| | |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u> </u>), <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Preliminary Amendment |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette | <input type="checkbox"/> pp. Amendment/Response |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing | <input type="checkbox"/> pp. Declaration/Exhibits |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input type="checkbox"/> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings | <input type="checkbox"/> pp. Appeal Brief (triplicate) |
| <input type="checkbox"/> pp. Assignment & Fee | <input checked="" type="checkbox"/> Issue Fee |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate) | <input type="checkbox"/> Notice of Appeal & Fee |
| <input type="checkbox"/> pp. Information Disclosure Statement & Fee with PTO-1449 and <input type="checkbox"/> references | <input type="checkbox"/> |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card
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Respectfully,
Genetics Institute, Inc.

Express Mail Label No. RB 793 965 512 45

PATENT

Serial No. 07/800,364 Doc. No. GT 51824 Atty/Sec. EK/06 Date 8/11/95
Inventor Rodney M. Henick et al.
Title PAV Encoding and Methods for Producing BMP-8

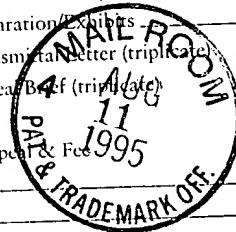
The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

| | |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u> </u>), <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Preliminary Amendment |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette | <input type="checkbox"/> pp. Amendment/Response |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing | <input type="checkbox"/> pp. Declaration/Exhibits |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input type="checkbox"/> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings | <input type="checkbox"/> pp. Appeal Brief (triplicate) |
| <input type="checkbox"/> pp. Assignment & Fee | <input checked="" type="checkbox"/> Issue Fee |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate) | <input type="checkbox"/> Notice of Appeal & Fee |
| <input type="checkbox"/> pp. Information Disclosure Statement & Fee with PTO-1449 and <input type="checkbox"/> references | <input type="checkbox"/> |

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Respectfully,
Genetics Institute, Inc.

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(5)

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Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rodney M. Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

For : DNA ENCODING AND METHODS
FOR PRODUCING BMP-8 PROTEINS

July 26, 1995

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

PETITION UNDER 37 C.F.R. §1.84(b)

Sir:

In accordance with the provision of 37 C.F.R. §1.84(b), Applicants hereby Petition the Commissioner to accept and consider the attached Photograph (Figure 1) in the above-identified application. The Applicants are submitting in triplicate the photograph developed on double weight photographic paper.

Applicants respectfully request that the Petition fee under 37 C.F.R. §1.17(h) for One Hundred Thirty Dollars (\$130) be charged to our Deposit Account No. 07-1060. Three copies of this Petition are enclosed for bookkeeping purposes.

SUBMITTED IN TRIPPLICATE

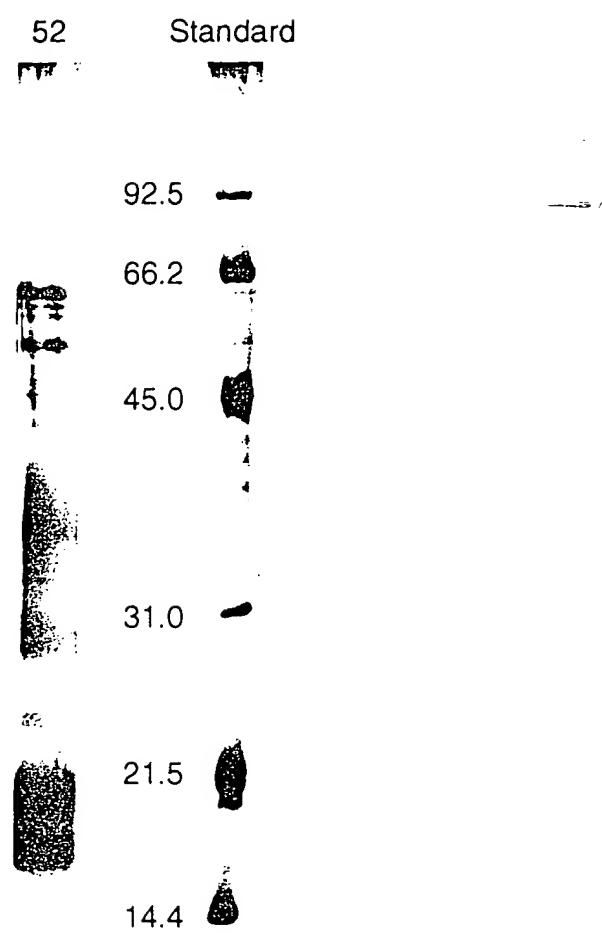
Respectfully submitted,

Date July 26, 1995

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617) 498-8622

Legal Affairs
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140

FIGURE 1



PATENT

Serial No. 07/1850, 364 Doc. No. 5182A Atty/Sec ER/DG Date July 31, 1995
Inventor Rodney M. Hewick et al
Title DATA AND METHODS FOR PRODUCING BMP-8 PROTEINS

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

| | |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u> </u>), <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Preliminary Amendment |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette | <input type="checkbox"/> pp. Amendment/Response |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing | <input type="checkbox"/> pp. Declaration/Exhibits |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input type="checkbox"/> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings | <input type="checkbox"/> pp. Appeal Brief (triplicate) |
| <input type="checkbox"/> pp. Assignment & Fee | <input type="checkbox"/> Issue Fee |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate) | <input type="checkbox"/> Notice of Appeal & Fee |

1.2 PTO-1449 under §184(b)

PATENT

Serial No. 07/1850, 364 Doc. No. 5182A Atty/Sec ER/DG Date July 31, 1995
Inventor Rodney M. Hewick et al
Title DATA AND METHODS FOR PRODUCING BMP-8 PROTEINS

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

| | |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u> </u>), <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Preliminary Amendment |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette | <input type="checkbox"/> pp. Amendment/Response |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing | <input type="checkbox"/> pp. Declaration/Exhibits |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input type="checkbox"/> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings | <input type="checkbox"/> pp. Appeal Brief (triplicate) |
| <input type="checkbox"/> pp. Assignment & Fee | <input type="checkbox"/> Notice of Appeal & Fee |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate) | <input type="checkbox"/> 3 copies of Photocopy of Figure 1 |
| <input type="checkbox"/> pp. Information Disclosure Statement (with PTO-1449 and <u> </u> references) | <input type="checkbox"/> in triplicate |

1.2 PTO-1449 under §184(b)

Inc.

1.2 PTO-1449 under §184(b)

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

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Genetics Institute, Inc.

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Ellen J. Kepinos

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Ellen J. Kepinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rodney M. Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

For : DNA ENCODING AND METHODS
FOR PRODUCING BMP-8 PROTEINS

July 26, 1995

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

AMENDMENT UNDER 37 C.F.R. §1.32 AND
RESPONSE TO REQUIREMENT FOR SUBSTITUTE DECLARATION

Sir:

Further to the telephone conference with Examiner Furman May 17, 1995, please amend the application as follows:

In the Specification:

Page 35, line 27, after "hH38." and before DNA, insert --Clone hH38 was deposited with the American Type Culture Collection (ATCC), Rockville, Maryland, under the accession number 69778 on March 30, 1995.--

REMARKS

It is understood that this amendment to reference the deposit number of clone hH38 does not raise any new matter issues.

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991
Page 2

The Notice of Allowability mailed May 15, 1995, indicates that the declaration filed January 24, 1992, lacks signature of the inventors. It is submitted that the declaration filed January 24, 1992, does include the signatures of each of the inventors. A copy of the declaration and the postcard are enclosed.

It is understood, therefore, that substitute declaration is not necessary. If this understanding is not correct, Applicants request the Examiner to notify Applicants:

Respectfully submitted,



Ellen J. Kepinos
Reg. No. 32,245
Attorney for Applicants
(617) 498-8622

Legal Affairs
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rodney M. Hewick et al

Serial No.: 07/800,364

Filed : November 26, 1991

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 24, 1992

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

RESPONSE TO NOTICE TO FILE MISSING PARTS
OF APPLICATION UNDER 37 C.F.R. 1.53(d)

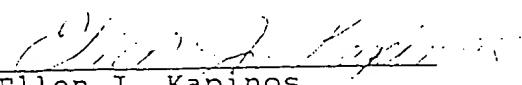
Sir:

In response to a Notice to File Missing Parts of Application under 37 C.F.R. Section 1.53(d) issued in connection with the above-identified application on January 6, 1992, Applicants hereby submit their Declaration and Power of Attorney pursuant to 37 C.F.R. Section 1.63.

The Declaration refers to the application's above-identified serial number and filing date. As indicated in the Notice, the deadline for submitting the Declaration is February 6, 1992.

Authorization is hereby given to charge the \$120 (One-hundred twenty dollar) surcharge under 37 C.F.R. Section 1.16(e) and any additional fees which may be required in this regard, and to credit any overpayment to Deposit Account No. 07-1060. Two duplicate copies of this letter are enclosed.

Respectfully submitted,


Ellen J. Kapinos
Registration No. 32,245
Genetics Institute, Inc.
87 Cambridge Park Drive
Cambridge, MA 02140-2387
Phone (617) 876-1170
Fax (617) 876-5851

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992.

I hereby certify that this correspondence is being
mailed with the United States Postal Service
as first class mail in an envelope addressed to Com-
missioner of Patents and Trademarks, Washing-
ton, D.C. 20231, on September 24, 1992
See my 3 pages

Docket No. GI 5182

Declaration and Power of Attorney

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am ~~the original, first and sole inventor (if only one name is listed below), or~~
an original, first and joint inventor (if plural names are listed below) of the subject
matter which is claimed and for which a patent is sought on the invention entitled:

BONE AND CARTILAGE INDUCTIVE PROTEINS

the specification of which: _____ is attached hereto.

X was filed on 11/26/91 as

Application Serial No. 07/800,364

and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified
specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information of which I am aware which is material
to the examination of this application in accordance with Title 37, Code of Federal
Regulations, section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, section 119
of any foreign application(s) for patent or inventor's certificate listed below and have
also identified below any foreign application for patent or inventor's certificate having
a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

| <u>Number</u> | <u>Country</u> | <u>Day/Month/Year Filed</u> | <u>Priority Claimed</u> |
|----------------|----------------|-----------------------------|-------------------------|
| PCT/US91/03388 | designated: | 15 May 1991 | <u>Yes/No</u> Yes |

I hereby claim the benefit under Title 35, United States Code, section 120 of any United
States Application(s) listed below and, insofar as the subject matter of each of the
claims of this application is not disclosed in the prior United States application in the
manner provided by the first paragraph of Title 35, United States Code, section 112, I
acknowledge the duty to disclose material information as defined in Title 37, Code of
Federal Regulations, section 1.56(a) which occurred between the filing date of the prior
application and the national or PCT international filing date of this application:

| <u>Application Serial No.</u> | <u>Filing Date</u> | <u>Status</u> |
|-------------------------------|--------------------|---------------|
| 07/525,357 | 16 May 1990 | Pending |
| 07/641,204 | 15 January 1991 | Pending |

*Austria, Belgium, Switzerland and Liechtenstein, Germany, France, United Kingdom,
Italy, Luxembourg, Netherlands, Sweden, Denmark, Spain, Greece, Japan, and Canada

Declaration and Power of Attorney
GI 5182A

I hereby appoint the following attorneys to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith, to file any International Applications which are based thereon under the provisions of the Patent Cooperation Treaty and to act on my behalf before the competent International Authorities: Bruce M. Elsen, Reg. No. 22,847; Thomas J. DesRosier, Reg. No. 30,168; Luann Cseri, Reg. No. 31,822; Ellen J. Kapinos, Reg. No. 32,245; and Patricia McDaniels, Reg. No. 33,194.

Address all correspondence to Legal Affairs Department, Genetics Institute, Inc., 87 Cambridge Park Drive, Cambridge, MA 02140. Telephone number: 617-876-1170.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Rodney M. Hewick

Inventor's signature R. M. Hewick

Citizenship GB Date: 1/24/92 Residence: 16 Woodcliffe Road
Lexington, MA 02173
USA

Post Office address (if different) _____

Full name of second joint inventor: Jack H. Wang

Inventor's signature J. H. Wang

Citizenship US Date: 1/24/92 Residence: 522 Lowell Street
Lexington, MA 02173
USA

Post Office address (if different) _____

Full name of third joint inventor: John M. Wozney

Inventor's signature John M. Wozney

Citizenship US Date: 1/24/92 Residence: 59 Old Bolton Road
Hudson, MA 01749
USA

Post Office address (if different) _____

Full name of fourth joint inventor Anthony J. CelesteInventor's signature Anthony J. CelesteCitizenship USDate 1/24/92Residence 86 Packard St., Hudson, MA 01749 USA

Post Office Address (if different) _____

Full name of fifth joint inventor _____

Inventor's signature _____

Citizenship _____ Date _____

Residence _____

Post Office Address (if different) _____

Full name of sixth joint inventor _____

Inventor's signature _____

Citizenship _____ Date _____

Residence _____

Post Office Address (if different) _____

PATENT

Serial No. 07/800,364 Doc. No. 5182A Atty/Sec. EK/EZ Date 1/24/92
Inventor Rudney M. Hewick et al
Title Bone + Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

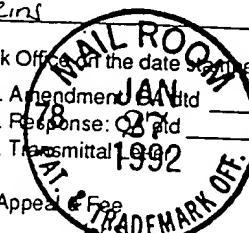
3 pp. Spec., ___ Claim, ___ Abstract
 pp. Declaration/Power of Attorney
 pp. Verified Statement (Small Entity)
 shts. Informal Drawings
 shts. Formal Drawings
 pp. Assignment
 pp. Preliminary Amendment
 pp. Extension of Time
 pp. Information Disclosure Statement
with PTO-1499 and ___ references

pp. Amendment 1A dtd 1/24/92
 pp. Response: Q3 dtd 1/24/92
 pp. Transmittal 1A dtd 1/24/92
 Issue Fee
 Notice of Appeal Fee
 Check # 1000 dtd 1/24/92
 Transmitted letter in triplicate
 Copy of Notice to file missing
Parts

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Sent via First Class mail

Respectfully,
Genetics Institute, Inc.



PATENT

Serial No. 07/180,364 Doc. No. 5182A Atty/Sec E.K. / D.E. Date July 31, 1995
Inventor Rodney M. Hewick et al
Title DNA Encoding and Methods for Producing

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

pp. Spec., claims (1-), Abstract

- pp. Preliminary Amendment
- pp. Amendment/Response
- pp. Declaration/Exhibits
- pp. Transmittal Letter (triplicate)
- pp. Appeal Brief (triplicate)

Issue Fee

Notice of Appeal & Fee
2 pp Amendment 5 1. ~~312~~ clm/
Response to Requirements
Substantive Requirements
by
fully requested to place its stamp on this postal card
5 pp Attachment

Respectfully,
Genetics Institute, Inc.

(att) *RP* *RP* *RP*
pp. 1

PATENT

Serial No. 07/180,364 Doc. No. 5182A Atty/Sec E.K. / D.E. Date July 31, 1995
Inventor Rodney M. Hewick et al

Title DNA Encoding and Methods for Producing

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

- pp. Spec., claims (1-), Abstract
- pp. Sequence ID Listing/Computer Diskette
- pp. Statement re Sequence ID Listing
- pp. Declaration/Power of Attorney
- shts. Informal/Formal Drawings
- pp. Assignment & Fee
- pp. Extension of Time & Fee (duplicate)
- pp. Information Disclosure Statement & Fee with PTO-1449 and references

- pp. Preliminary Amendment
- pp. Amendment/Response
- pp. Declaration/Exhibits
- pp. Transmittal Letter (triplicate)
- pp. Appeal Brief (triplicate)
- Issue Fee

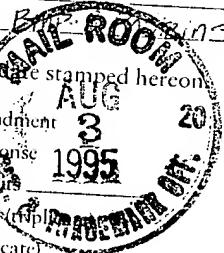
Notice of Appeal & Fee

2 pp Amendment 5 1. ~~312~~ and
Response to Requirements
Substantive Requirements
by
Signature Declaration

5 pp Attachment
Respectfully,
Genetics Institute, Inc.

Express Mail Label No. _____

Certificate of Service
MPL

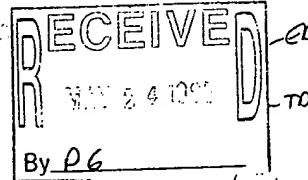




UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS,
Washington, D.C. 20231

7

| | | | |
|---------------|-------------|-----------------------|---------------------|
| SERIAL NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|---------------|-------------|-----------------------|---------------------|



NOTICE OF ALLOWABILITY

8/15/95 IF / Formal Drawings / Decl.

PART I.

- This communication is responsive to Serial D-16 1-131-35
- All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
- The allowed claims are 7, 8, 14 and 15
- The drawings filed on _____ are acceptable.
- Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [] been received. [] not been received. [] been filed in parent application Serial No. _____, filed on _____.
- Note the attached Examiner's Amendment.
- Note the attached Examiner Interview Summary Record, PTOL-413.
- Note the attached Examiner's Statement of Reasons for Allowance.
- Note the attached NOTICE OF REFERENCES CITED, PTO-892.
- Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

- Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED. *1-24-92*
- APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
 - Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. 15. CORRECTION IS REQUIRED.
 - The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
 - Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
 - Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- Examiner's Amendment
- Examiner Interview Summary Record, PTOL-413
- Reasons for Allowance
- Notice of References Cited, PTO-892
- Information Disclosure Citation, PTO-1449
- Notice of Informal Application, PTO-152
- Notice re Patent Drawings, PTO-948
- Listing of Bonded Draftsmen
- Other *Copy of PTO-152*

KEITH C. FURMAN
PRIMARY EXAMINER
GROUP 1800



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

18M2/0515

LEGAL AFFAIRS DEPT.
GENETICS INSTITUTE, INC.
10 CAMPBELL PARK DR.
CAMBRIDGE, MA 02140

NOTICE OF ALLOWANCE
AND ISSUE FEE DUE

Note attached communication from the Examiner
 This notice is issued in view of applicant's communication filed _____

| SERIES CODE/SERIAL NO. | FILING DATE | TOTAL CLAIMS | EXAMINER AND GROUP ART UNIT | DATE MAILED |
|--------------------------|--|--------------|--------------------------------|--------------|
| 67-17704-1000 | 12/10/1980 | 100 | PTO/Office of the Commissioner | 12/12/1980 |
| First Named Applicant | THE INVENTION | | | |
| TITLE OF INVENTION | DNA ENZYME (DNA) AND METHODS FOR PRODUCING AND PURIFYING DNA CAMS AMENDMENT | | | |
| ATTY'S DOCKET NO. | CLASS-SUBCLASS | BATCH NO. | APPLN. TYPE | SMALL ENTITY |
| | | | | |

THE APPLICATION IDENTIFIES ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT.
PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

- I. Review the SMALL ENTITY Status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
 - A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
 - B. If the Status is the same, pay the FEE DUE shown above.
- II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.
- III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
- B. File verified statement of Small Entity Status before, or with, pay of 1/2 the FEE DUE shown above.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS,
Washington, D.C. 20231

| SERIAL NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKETT NO. |
|---------------|-------------|-----------------------|----------------------|
|---------------|-------------|-----------------------|----------------------|

EXAMINER

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

28

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) John Weyant (3)

(2) John Weyant (4)

Date of interview 2-23-95

Type: Telephonic Personal (copy is given to applicant applicant's representative).

Exhibit shown or demonstration conducted: Yes No. If yes, brief description: _____

Agreement was reached with respect to some or all of the claims in question. was not reached.

Claims discussed: all pending

Identification of prior art discussed: none

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: 147 merges into

the claims are allowed

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

Examiner's Signature John Weyant

Date of Transmission Jan. 31, 1995 Telex No. 1-703-308-4227

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patents and Trademark Office on the date indicated above.

Date of Deposit January 31, 1995

I hereby certify that this correspondence is being deposited with the U.S. Postal Service under 37 CFR §1.8 in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date of deposit as indicated above.

(8)

GI 5182A

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS

WASHINGTON, D.C. 20231

ATTN: Application Processing Division

Special Processing and Correspondence Branch

Ellen J. Kapinos

SERIAL NO.: 07/800,364
FILED: November 26, 1991
GROUP ART UNIT: 1814

SIR:

In re application of: Rodney M. Hewick et al.

Entitled: DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS

Transmitted herewith is an Amendment (4 pages) in the above-identified application. The following checked items are applicable:

A Petition for Extension of Time for _____ months is hereby made, under §1.136(a) and the fee is calculated herein.

| CLAIM TYPE | CLAIMS AFTER AMENDMENT MINUS PRIOR PAID CLAIMS | EQUALS PRESENT EXTRA CLAIMS | RATE | FEE |
|---|---|--------------------------------|--------------|-----|
| Independent | 2 - 13 | - | x \$76 = | \$0 |
| Total | 2 - 25 | - | x \$22 = | 0 |
| <input type="checkbox"/> Multiple Dependent Claims (1st presentation) | | | +\$240 | 0 |
| | | | SUBTOTAL FEE | \$0 |
| Fee for Petition for Extension | | | | 0 |
| TOTAL FEE | | | | \$0 |

The Commissioner is hereby authorized to charge payment of \$ _____ under §1.16 associated with this communication or credit any overpayment to Deposit Account No. 07-1060.

No additional fee is believed due; however, if any fee should be due, authorization is hereby given to charge it to Deposit Account 07-1060.

SUBMITTED IN TRIPPLICATE

Respectfully submitted,

Ellen J. Kapinos

Ellen J. Kapinos

Reg. No. 32,245

Attorney of Record

LEGAL AFFAIRS

GENETICS INSTITUTE, INC.

87 Cambridge Park Drive

Cambridge, Massachusetts 02140

Telephone: (617) 498-8622

Faxsimile: (617) 876-5851

Dated: January 30, 1995

CERTIFICATE OF FACSIMILE TRANSMISSION

Date of Transmission

Jan 31, 1995 *Telex No. 1-703-308-4227*

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office on the date indicated above.

Ellen J. Karpinski

CERTIFICATE OF MAILING

Date of Deposit

January 31, 1995

I hereby certify that this correspondence is being deposited with the U.S. Postal Service under 37 CFR §1.8 in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date of deposit as indicated above.

Ellen J. Karpinski

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rodney M. Hewick, et al.

Serial No. : 07/800,364

Filed : November 26, 1991

For : DNA ENCODING AND METHODS
FOR PRODUCING BMP-8 PROTEINS

January 30, 1995

Art Unit: 1814

Examiner: K. Furman

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

AMENDMENT

Sir:

This is in response to the Advisory Action mailed November 8, 1994, and the telephone conference with Examiner Furman January 5, 1995. Please amend the application as follows:

In the Claims:

Cancel claims 6, 9, 13, 16-19, 26-33 and 35.

7. (third amendment) An isolated DNA sequence selected from the group consisting of
[comprising]

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991
Page 2

(a) the nucleotide sequence set forth in SEQ ID NO:13 [from] comprising nucleotide #8 to #850; and

(b) nucleotide sequences which encode the amino acid sequence comprising amino acid #139 to #142 of SEQ ID NO:14.

8. (third amendment) An isolated DNA sequence selected from the group consisting of [comprising]

(a) the nucleotide sequence set forth in SEQ ID NO:13 [from] comprising nucleotide #434 to #850; and

(b) nucleotide sequences which encode the amino acid sequence comprising amino acid #4 to #142 of SEQ ID NO:14.

REMARKS

Reconsideration of the application and entry of the amendments is requested. Claims 6, 9, 13, 16-19, 26-33 and 35 have been deleted in order to advance prosecution. By deletion of these claims, Applicants do not acquiesce in the outstanding rejections and reserve the right to pursue the subject matter of these claims in one or more continuing applications.

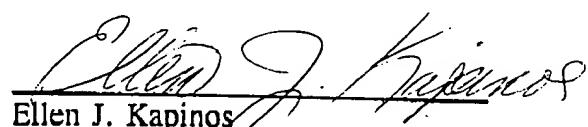
Claims 7 and 8 and 14 and 15 dependent thereon have been amended to include degenerate sequences as suggested by the Examiner. Basis for this amendment appears on page 6, lines 1-5 and 25-28 and page 10, lines 19-29. Claims 7, 8, 14 and 15 remain in the application and are set forth in attached Appendix A.

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991
Page 3

In view of the above, it is submitted that the claims as amended are in condition for allowance. Reconsideration of the rejections and objections is requested. Should the Examiner believe that a telephone interview would assist in clarifying any remaining issues, Applicants respectfully invite the Examiner to call the undersigned attorney at the telephone number provided below.

Respectfully submitted,

Date January 31, 1995


Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617) 498-8622

Legal Affairs
Genetics Institute, Inc.
87 Cambridge Park Drive
Cambridge, MA 02140

APPENDIX A

7. An isolated DNA sequence selected from the group consisting of
 - (a) the nucleotide sequence set forth in SEQ ID NO:13 comprising nucleotide #8 to #850; and
 - (b) nucleotide sequences which encode the amino acid sequence comprising amino acid #139 to #142 of SEQ ID NO:14.
8. An isolated DNA sequence selected from the group consisting of
 - (a) the nucleotide sequence set forth in SEQ ID NO:13 comprising nucleotide #434 to #850; and
 - (b) nucleotide sequences which encode the amino acid sequence comprising amino acid #4 to #142 of SEQ ID NO:14.

14. A host cell transformed with the DNA of claim 7.

15. A host cell transformed with the DNA of claim 8.

PATENT

Serial No. 07/180,344 Doc. No. 5182 A Atty/Sec EK/DG Date 1-31-95

Inventor Rodney Itewick et al

Title DNA Encoding and Methods for Producing
BMP-8 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon:

| | |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u> </u>), <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Preliminary Amendment |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette | <input checked="" type="checkbox"/> <u>H</u> pp. Amendment/Response |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing | <input type="checkbox"/> pp. Declaration/Exhibits |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input checked="" type="checkbox"/> <u>1</u> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings | <input type="checkbox"/> pp. Appeal Brief (triplicate) |
| <input type="checkbox"/> pp. Assignment & Fee | <input type="checkbox"/> Issue Fee |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate) | <input type="checkbox"/> Notice of Appeal & Fee |
| <input type="checkbox"/> pp. Information Disclosure Statement & Fee with PTO-1449 and <input type="checkbox"/> references | |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card
and place it in the outgoing mail.

Respectfully,
Genetics Institute, Inc.

PATENT

Serial No. 07/180,344 Doc. No. 5182 A Atty/Sec EK/DG

Inventor Rodney Itewick et al

Title DNA Encoding and Methods for Producing
BMP-8 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

| | |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u> </u>), <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Preliminary Amendment |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette | <input checked="" type="checkbox"/> <u>H</u> pp. Amendment/Response |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing | <input type="checkbox"/> pp. Declaration/Exhibits |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input checked="" type="checkbox"/> <u>1</u> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings | <input type="checkbox"/> pp. Appeal Brief (triplicate) |
| <input type="checkbox"/> pp. Assignment & Fee | <input type="checkbox"/> Issue Fee |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate) | <input type="checkbox"/> Notice of Appeal & Fee |
| <input type="checkbox"/> pp. Information Disclosure Statement & Fee with PTO-1449 and <input type="checkbox"/> references | |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card
and place it in the outgoing mail.

Respectfully,
Genetics Institute, Inc.

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9

| SERIAL NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|---------------|-------------|-----------------------|---------------------|
| 07/800,364 | 11/26/91 | HEWICK | R 5182A |

18ME2/1108

FURMAN

PAPER NUMBER

1814

25

DATE

11/08/94

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

THE PERIOD FOR RESPONSE:

a) is extended to run _____ or continues to run _____ from the date of the final rejection
b) expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

Appellant's Brief is due in accordance with 37 CFR 1.192(a).

Applicant's response to the final rejection, filed 10-5-94 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. The proposed amendments to the claim and/or specification will not be entered and the final rejection stands because:
 - a. There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.
 - b. They raise new issues that would require further consideration and/or search. (See Note).
 - c. They raise the issue of new matter. (See Note).
 - d. They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
 - e. They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE:

2. Newly proposed or amended claims 9 and 35 would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. Upon the filing an appeal, the proposed amendment will be entered will not be entered and the status of the claims will be as follows:

Claims allowed: 6-7, 9, 14, 15, and 35

Claims objected to: none

Claims rejected: 6, 13, 16-19 and 26-33

However;

Applicant's response has overcome the following rejection(s): The rejection set forth in Paragraph 5 is withdrawn.

4. The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because while the claims no longer read upon, no particular species it would still require undue expenditure to determine what were active for the reasons previously discussed, which reasons have not been addressed by applicant. See also Grant Patent, 27 USPQ2d 1662 (1993) which supports and/or supplements the technical arguments. Claims or methods of making may not be "burden" rejection, presented.

The proposed drawing correction has has not been approved by the examiner.

Other applicants are correct and thanked for noting that the omission of claim 28 from the scope of claim 26 was unintentional and/or it was, in fact, a typographical error as can be seen from the fact that the scope of the claims as in the other claims of the application. Keith K. Furman
The formal drawings are not accepted for the reasons stated on the attached PTO-948.



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EXAMINER

| | |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
|----------|--------------|

24

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Ellen Kaganer (3) _____

(2) Caroline Toman (4) _____

Date of Interview 10-3-94

Type: Telephonic Personal (copy is given to applicant applicant's representative).

Exhibit shown or demonstration conducted: Yes No. If yes, brief description: _____

Agreement was reached with respect to some or all of the claims in question. was not reached.

Claims discussed: none

Identification of prior art discussed: none

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Caroline stated that

st. after final had been received.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., Items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftpersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date) 10-5-94 are
 A. not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.
 B. objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings:
 Black ink. Color.
 Not black solid lines. Fig(s) _____
 Color drawings are not acceptable until petition is granted.
2. PHOTOGRAPHS. 37 CFR 1.84(b)
 Photographs are not acceptable until petition is granted.
3. GRAPHIC FORMS. 37 CFR 1.84 (d)
 Chemical or mathematical formula not labeled as separate figure. Fig(s) _____
 Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis. Fig(s) _____
 Individuals waveforms not identified with a separate letter designation adjacent to the vertical axis. Fig(s) _____
4. TYPE OF PAPER. 37 CFR 1.84(e)
 Paper not flexible, strong, white, smooth, nonshiny, and durable. Sheet(s) _____
 Erasures, alterations, overwritings, interlineations, cracks, creases, and folds not allowed. Sheet(s) _____
5. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable paper sizes:
 21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)
 21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)
 21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)
 21.0 cm. by 29.7 cm. (DIN size A4)
 All drawing sheets not the same size. Sheet(s) _____
 Drawing sheet not an acceptable size. Sheet(s) _____
6. MARGINS. 37 CFR 1.84(g): Acceptable margins:
 Paper size _____

| | | | |
|---------------------|---------------------|---------------------|-------------------|
| 21.6 cm. X 35.6 cm. | 21.6 cm. X 33.1 cm. | 21 cm. X 27.9 cm. | 21 cm. X 29.7 cm. |
| (8 1/2 X 14 inches) | (8 1/2 X 13 inches) | (8 1/2 X 11 inches) | (DIN Size A4) |
| T 5.1 cm. (2") | 2.5 cm. (1") | 2.5 cm. (1") | 2.5cm. |
| L .64 cm. (1/4") | .64 cm. (1/4") | .64 cm. (1/4") | 2.5 cm. |
| R .64 cm. (1/4") | .64 cm. (1/4") | .64 cm. (1/4") | 1.5 cm. |
| B .64 cm. (1/4") | .64 cm. (1/4") | .64 cm. (1/4") | 1.0 cm. |

 Margins do not conform to chart above.
 Sheet(s) _____
 Top (T) _____ Left (L) _____ Right (R) _____ Bottom (B) _____
7. VIEWS. 37 CFR 1.84(h)
 REMINDER: Specification may require revision to correspond to drawing changes.
 All views not grouped together. Fig(s) _____
 Views connected by projection lines. Fig(s) _____
 Views contain center lines. Fig(s) _____
- Partial views. 37 CFR 1.84(h)(2)
 Separate sheets not linked edge to edge. Fig(s) _____
 View and enlarged view not labeled separately. Fig(s) _____
 Long view relationship between different parts not clear and unambiguous. 37 CFR 1.84(h)(2)(ii)
 Fig(s) _____
- Sectional views. 37 CFR 1.84(h)(3)
 Hatching not indicated for sectional portions of an object. Fig(s) _____
 Hatching of regularly spaced oblique parallel lines not spaced sufficiently. Fig(s) _____
 Hatching not at substantial angle to surrounding axes or principal lines. Fig(s) _____
 Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s) _____
 Hatching of juxtaposed different elements not angled in a different way. Fig(s) _____
- Alternate position. 37 CFR 1.84(h)(4)
 A separate view required for a moved position. Fig(s) _____

- Modified forms. 37 CFR 1.84(h)(5)
 Modified forms of construction must be shown in separate views. Fig(s) _____
8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
 View placed upon another view or within outline of another. Fig(s) _____
 Words do not appear in a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) _____
9. SCALE. 37 CFR 1.84(j)
 Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s) _____
 Indication such as "actual size" or "scale 1/2" not permitted. Fig(s) _____
 Elements of view not in proportion to each other. Fig(s) _____
10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(k)
 Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings). Fig(s) _____
11. SHADING. 37 CFR 1.84(m)
 Shading used for other than shape of spherical, cylindrical, and conical elements of an object, or for flat parts. Fig(s) _____
 Solid black shading areas not permitted. Fig(s) _____
12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
 Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(1) Fig(s) _____
 Numbers and reference characters used in conjunction with brackets, inverted commas, or enclosed within outlines. 37 CFR 1.84(p)(1) Fig(s) _____
 Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(1) Fig(s) _____
 English alphabet not used. 37 CFR 1.84(p)(2) Fig(s) _____
 Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s) _____
13. LEAD LINES. 37 CFR 1.84(q)
 Lead lines cross each other. Fig(s) _____
 Lead lines missing. Fig(s) _____
 Lead lines not as short as possible. Fig(s) _____
14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
 Number appears in top margin. Fig(s) _____
 Number not larger than reference characters. Fig(s) _____
 Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s) _____
15. NUMBER OF VIEWS. 37 CFR 1.84(u)
 Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) _____
 View numbers not preceded by the abbreviation Fig. Fig(s) _____
 Single view contains a view number and the abbreviation Fig. Fig(s) _____
 Numbers not larger than reference characters. Fig(s) _____
16. CORRECTIONS. 37 CFR 1.84(w)
 Corrections not durable and permanent. Fig(s) _____
17. DESIGN DRAWING. 37 CFR 1.152
 Surface shading shown not appropriate. Fig(s) _____
 Solid black shading not used for color contrast. Fig(s) _____



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07/800,364 11/26/91 HEWICK

P 51826

EXAMINER

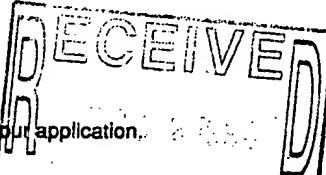
FIRMAN, K

18M2/0407

ART UNIT PAPER NUMBER

18

LEGAL AFFAIRS DEPT.
GENETICS INSTITUTE, INC.
87 CAMBRIDGE PARK DR.
CAMBRIDGE, MA 02140



1814

DATE MAILED:

04/07/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

-5K

-TD

7/7/94 Notice of
Appeal (3rd m.)

This application has been examined

Responsive to communication filed on

6/7/94 Final OA (and month)
10/7/94 (and month)
13/94

This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- Notice of References Cited by Examiner, PTO-892.
- Notice of Draftsman's Patent Drawing Review, PTO-948.
- Notice of Art Cited by Applicant, PTO-1449.
- Notice of Informal Patent Application, PTO-152.
- Information on How to Effect Drawing Changes, PTO-1474.
- _____

Part II SUMMARY OF ACTION

1. Claims 1-35 are pending in the application.

Of the above, claims 1-5, 10-12 and 20-25 and 34 are withdrawn from consideration.

2. Claims _____ have been cancelled.

3. Claims 7, 8, 14 and 15 are allowed.

4. Claims 6, 9, 13, 16-19 and 26-33 and 35 are rejected.

5. Claims _____ are objected to.

6. Claims 34 are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been approved by the examiner; disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).

12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the provisions of 37 C.F.R. 1.116. A certificate of mailing can be filed in accordance with 37 C.F.R. 1.108.

Part III DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §1.821(a) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 CFR §§ 1.821 through 1.825 as follows: This application does not conform exclusively to the requirements of §§ 1.821 through 1.825. The non-conforming material should be deleted (§ 1.821(b)). The bovine sequence of native BMP-8 set forth on p. 33 in Table 4, while identified with regard to the sequence differences from the human homolog with respect to SEQ ID NO: 14 on p. 32 and not required for examination, must either be deleted or, preferably, a new Sequence Listing and CRF must be provided including this sequence since the sequence is actually shown on p. 33 of the specification. All sequences actually shown should be in the Sequence Listing.

RESPONSE TO AFFIRMATION OF RESTRICTION REQUIREMENT

2. Applicant's election without traverse of Group II in Paper No. 15 is acknowledged.

Claims 1-5, 10-12 and 20-25 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Election was made without traverse in Paper No. 15.

While applicants state at the bottom of p. 10 of the instant amendment that claims 1-5, 10-12 and 20-25 have been deleted, there is no specific amendment directing the cancellation of these claims and it is stated at the bottom of p. 11 that the claims are merely "withdrawn". Clarification is requested.

Newly submitted claim 34^{is} directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The Invention of the instant DNAs, host cells and methods of producing BMP-8 proteins and the invention of

new claim 34 directed to a method for isolating a DNA sequence (separately classified in Class 435, subclass 6) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the products can be used to produce the BMP-8 protein for use as a drug.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 34 is also withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

OBJECTIONS/REJECTIONS WITHDRAWN

3. The specification is objected to under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 24 of the last Office Action, is withdrawn in view of the instant amendments and applicants' arguments.

The rejection of Claims 17 and 18 under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 26 of the last Office Action, is withdrawn in view of the instant amendments.

The objection to the specification and rejection of claims 9 and 18 under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 27 and 28 of the last Office Action, is withdrawn in view of the instant Declaration of Deposit Requirement including the required statements by the attorney of record.

The rejection of Claims 6-8, 13-15 and 19 under 35 U.S.C. § 112, second paragraph, as set forth in paragraph 29 of the last Office Action, is withdrawn in view of the instant amendments.

The rejection of Claims 6, 9, 13 and 16 under 35 U.S.C. § 101, as set forth in paragraph 32 of the last Office Action, is withdrawn in view of the instant amendments and applicants' arguments.

NEW OBJECTIONS/REJECTIONS

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 9, 16, 18 and 35 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 and those dependent thereon are indefinite and/or not enabled because that deposited as ATCC #75010 and #75011 are microorganisms having numerous DNAs and it is unclear which DNA applicants are referring to. The specification does not enable how to make and use the broad scope of all isolated DNAs of the deposited microorganism because the function of such DNAs and the proteins encoded is not disclosed or supported with respect to how to make and use them without undue experimentation. Additionally, claim 18 now expectedly reads upon a significant number of inoperative species because those skilled in the art would question whether the proteins encompassed in general would have the useful activity of the native BMP-8 protein having the native sequence for the reasons

previously discussed. Broad claim may be rejected merely because it reads on a significant number of inoperative species when examiner sets forth reasonable grounds in support of his or her conclusions that the claims may read upon inoperative subject matter and it becomes incumbent upon applicant either to reasonably limit claims to approximate area where operativeness has not been challenged or to rebut examiner's challenge by submission of representative evidence or by persuasive arguments based on known laws of physics and chemistry (see In re Cook and Merigold, 169 USPQ 298 (CCPA 1971)).

6. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 17-19, 26, 27 and 33 rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent 4,886,747 of Derynck et al. (AS). Derynck (cited by applicants after the first action) discloses the recombinant expression of TGF- β comprising culturing a cell transformed with a vector comprising a DNA encoding TGF- β in operative association with expression control sequences an the recovery, isolation and purification of the protein encoded by the DNA from the culture media (see Example 5). While Derynck et al. did not disclose the DNAs or proteins of the claims, claims 17-19, 26, 27 and 33 are drawn to the use of a new but similar product in an old process

of making which is not a patentably different process because the only difference between the process known in the art and the claimed process is the new product of applicants' claimed invention which would have been expected to work in the known process. See In re Durden 226 U.S.P.Q. 359 (Fed. Cir. 1985) and Ex parte Ochiai, 24 USPQ2d 1265 (BPAI, 1992). See also columns 19-21 of Kuberanpath et al. (AT) and col. 33 of Parsons et al. (which references are not required and not relied upon in the rejection but cited as further evidence) which further show that sequences of the family of proteins to which the instant sequence(s) belongs would have been expected to work in the known process, especially in view of the known homology between the members of this family and TGF- β .

OBJECTIONS/REJECTIONS MAINTAINED

7. Applicant's arguments filed 1-13-93 have been fully considered but they are not deemed to be persuasive.

8. The rejection of Claims 6, 13 and 17 (now Claims 6, 13, 17, 29-33 and 35) under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to where the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2, as set forth in paragraph 25 of the last Office Action is again made and maintained.

Applicants' arguments are on the grounds that the limitation to include all of a), b) and c) which form part of the nucleotide sequence of BMP-8 should be enabled and obviate the rejection. However, these arguments are not persuasive because this is not what the Examiner had set forth as being enabled and applicants have not addressed the Examiner's arguments with regard to why that which is now claimed should be enabled in spite of those arguments. Further, the sequences of the claim are not known to be particularly correlated with the activity of the intact protein and it has not been shown that a protein merely containing these portions would have the requisite activity.

Additionally, even if such correlation and activity were shown, those skilled in the art would question whether these sequences in any order would produce an active protein due to possible steric hindrances, improper folding and/or incorrect juxtapositioning of critical regions. The limitations to include molecular weight limits does not narrow the scope so as not to require undue experimentation since the intervening portions which are not in the required portions (which can be any sequence) still encompasses an extremely large or essentially infinite number of species combinations and includes regions which may be required for useful activity. Additionally, claim 17 now expectedly reads upon a significant number of inoperative species because those skilled in the art would question whether the proteins encompassed in general would have the useful activity of the native BMP-8 protein having the native sequence for the reasons previously discussed.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. Claims 7, 8, 14 and 15 are allowed.

11. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE

EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Papers relating to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April 6, 1994

Keith Furman
KEITH C. FURMAN, Ph.D.
PRIMARY EXAMINER
GROUP 1800



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

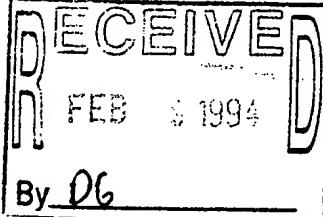
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11

| SERIAL NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
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| 07/300,364 | 11/26/93 | HEWLETT | R 510022 |

LEGAL AFFAIRS DEPT.
GENETICS INSTITUTE, INC.
87 CAMBRIDGE PARK DR.
CAMBRIDGE, MA 02140

18M2/0207



| EXAMINER | |
|------------|--------------|
| FLICKINGER | |
| ART UNIT | PAPER NUMBER |

DATE MAILED:

02/07/94

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

The holding of abandonment mailed 9-14-93, has been withdrawn.

The copy of the response filed 8-4-93, has been made of record in the file.

The application has been returned to pending status.


Donna Chapman, Deputy Supervisory Application Examiner
Patent Examining Group 1800

HONORABLE COMMIS. ^{ON} OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

SERIAL NO.: 07/800,364
FILED: November 26, 1991
GROUP ART UNIT: 1814

SIR:

In re application of: Rod Hewick et al.

Entitled: BONE AND CARTILAGE INDUCTIVE PROTEINS

Transmitted herewith is an Amendment in the above-identified application. The following checked items are applicable:

A Petition for Extension of Time for 3 months is hereby made, under §1.136(a) and fee is calculated herein;

Other: *Notice of Appeal*

*Response to Notice and Submission of Formal Drawings w/ Form 948
Sequence Listing, Dicrete, Statements Under 1.825 (b) and (a)*

| Claims after amendment | Minus Prior PAID claims | Equals present extra claims | RATE | Fee |
|--|-------------------------|-----------------------------|----------------------|-----------|
| Independent | - 13 | = | x \$74.00 = | \$.00 |
| Total | - 25 | = | x \$22.00 = | \$.00 |
| [] Multiple Dependent Claims (1st presentation) | | | +\$230.00 | \$.00 |
| <i>[XX] Notice of Appeal</i> | | | +\$280.00 | \$ 280.00 |
| | | | SUBTOTAL FEE | \$.00 |
| <input checked="" type="checkbox"/> Petition for Extension of time fee pursuant to §1.17 | | extension within 3 months | | \$870.00 |
| | | | TOTAL ADDITIONAL FEE | \$1150.00 |

The fee has been calculated above; The Commissioner is hereby authorized to charge payment of \$1150.00 under §1.16 associated with this communication or credit any overpayment to Deposit Account No. 07-1060.

[] No additional fee is believed due.

CERTIFICATE OF MAILING "EXPRESS MAIL" NUMBER RB 793967900 US

Date of Deposit *October 5 1991*

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Ellen J. Kapinos

Ellen J. Kapinos
Attorney of Record: Ellen J. Kapinos
Registration No. 32,245

SUBMITTED IN TRIPPLICATE

Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140

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and is addressed to Honorable Commissioner of Patents and
Trademarks, Washington, D.C. 20231 on October 5, 1994.

By Ellen J. Kapinos
Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick et al.

Serial No. : 07/800,364 Examiner : K. Kurman

Filed : November 26, 1991 Art Unit : 1814

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

PETITION AND FEE FOR EXTENSION OF TIME UNDER 37 CFR 1.136

We hereby request an extension of time for response of three (3) month/s pursuant to 37 CFR 1.136(a) in which to respond to the Office Action mailed April 7, 1994. This extension resets the time for response from July 7 to October 7, 1993.

We authorize the charging of Eight Hundred and Seventy (\$870.00) and any additional fees and crediting of overpayment to our Deposit Account 07-1060, and for this purpose, we enclose a duplicate copy of this petition.

Respectfully submitted,

October 4, 1994
Date

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617)-876-1170
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140-2387

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
GROUP ART UNIT:1814

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By Ellen J. Kapinos
Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Hewick et al Group Art Unit: 1814

Serial No. : 07/800,364 Examiner: K. Furman

Filed : November 26, 1991

For : DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS

BOX AF
Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

RESPONSE UNDER 37 CFR 1.116

Sir:

This is in response to the Office Action mailed April 7. A Request for a Three Month Extension and Fee accompanies this Response. The Extension resets the time for response from July 7 to October 7, 1994.

Please amend the application as follows:

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In the Specification:

Page 32, line 7, after "Table 4" insert --(SEQ ID NO: 15)--.
Page 33, line 23, after "Table 4" insert --(SEQ ID NO:15)--.
Pages 41-48, delete the Sequence Listing and replace it with the
enclosed Sequence Listing pages 41-53.

In the Claims:

Cancel claims 1-5, 10-12, 20-25, and 34.

6. (twice amended) An isolated DNA sequence encoding a BMP-8 protein comprising the following sequences

a)

GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC
ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC
GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC
CAC (SEQ ID NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG
GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC
ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID
NO: 11)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

9. (twice amended) An isolated DNA comprising the [DNA] nucleotide sequence of ATCC #75010 encoding BMP-8.

17. (twice amended) A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

18. (twice amended) A method comprising the steps of

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

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28. (once amended) An isolated DNA sequence encoding a BMP-8
protein comprising the following amino acid sequences:

a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-
Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:1);

b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3)

said BMP-8 protein characterized by the ability to induce the
formation of cartilage and/or bone.

35. (once amended) An isolated DNA [sequence] comprising the
nucleotide sequence of ATCC #75011 encoding BMP-8.

REMARKS

Reconsideration of the application and entry of the
amendments is requested. The following documents accompany this
response:

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1. Transmittal Letter
2. Petition for Extension and Required Fee
3. Appendix A - Claims
4. Substitute Sequence Listing (pages 41-53)
5. Diskette containing computer readable Sequence Listing (CRF)
6. Statement Pursuant to 37 CFR 1.825(a) and 1.825(b)
7. Notice of Appeal
8. Drawing

A new Sequence Listing along with the CRF and statements in accordance with 37 CFR 1.821-1.825 are provided. The Sequence Listing has been amended to include the bovine sequence of BMP-8 set forth on page 33, Table 4 as SEQ ID NO: 15. The specification has been amended to reference SEQ ID NO:15. It is understood that the application now complies with the requirements of 37 CFR 1.821 through 1.825.

The application has been amended directing cancellation of claims 1-5, 10-12, 20-25, and 34 as these claims have been withdrawn from further consideration by the Examiner. Applicants hereby preserve their rights to pursue the subject matter contained in these withdrawn claims in one or more divisional applications filed pursuant to 35 U.S.C. 121. It is believed that the inventorship remains the same despite the withdrawal of non-elected claims. Claims 6, 9, 17, 18, 28 and 35 have been amended. The claims as amended appear in Appendix A.

Corrected formal drawings are submitted herewith.

WO 92/07073 cited as Foreign Patent Document "BM" on PTO form 1449 submitted with the amendment filed August 4, 1993 discloses an "OP-2" protein with sequence which corresponds to BMP-8 nucleotide and amino acid sequence.

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Rejections Based on 35 USC §112

Claims 9, 16, 18 and 35 are rejected for lack of enablement and/or failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the Examiner, it is unclear which DNA of the deposited microorganisms is claimed. Claim 18 is further rejected for reading on inoperative species because one skilled in the art would question whether the proteins encompassed in general would have the useful activity of the native BMP-8 protein. Claim 9 and claims 16 and 18 dependent thereon and 35 have been amended to recite that the claimed sequence of the deposit is the nucleotide sequence encoding BMP-8. Basis for the amendments appears on page 34, lines 22-24 and page 28, lines 30 -32. Claim 18 has been further amended to characterize the recovered protein by the ability to induce the formation of cartilage and/or bone. It is understood that these claims are definite and enabling as they are directed to the BMP-8 sequence of the deposited microorganism. It is understood that claim 18 no longer reads on a significant number of inoperative species because step (b) is directed to the recovery of the protein encoded by the DNA of step (a) and having the functional limitation of the ability to induce cartilage and/or bone formation.

The rejection of claims 6,13 and 17 (now claims 6,13,17,29-33 and 35) because the disclosure is enabling only for claims limited to those wherein the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2, has been maintained. [In response Applicants have assumed that the Examiner intended

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to include claim 28 in this grouping and request the Examiner to notify Applicants if this is not correct.] Claim 6 as amended recites a DNA encoding a BMP-8 protein comprising three sequences [a), b) and c)] which form part of the nucleotide sequence encoding BMP-8 and further recites the functional limitation of the recovered protein to induce the formation of cartilage and/or bone. Claim 28 has been similarly amended. It is submitted that the scope of claims 6, 28 and 13, 17, and 29-33 dependent thereon which are limited to a sequence comprising the sequences of a), b) and c) and encode a protein having the ability to induce the formation of cartilage and/or bone is reasonably correlated with the scope of enablement. Claim 17 has been further amended to include the characterization of the recovered protein by the ability to induce the formation of cartilage and/or bone. Therefore, it is submitted that claim 17 does not read on a significant number of inoperative species because those skilled in the art would be able to determine whether the recovered protein was active by its ability to induce cartilage and/or bone formation. It is therefore submitted that the claims are enabled by the disclosure.

Rejections Based on 35 USC §103

Claims 17-19, 26, 27 and 33 are rejected as unpatentable over Derynck et al., US 4,886,747. Derynck discloses the recombinant expression of TGF- β comprising culturing a cell transformed with a vector comprising a DNA encoding TGF- β and the recovery, isolation and purification of the protein. The Examiner contends that while Derynck et al. do not disclose the DNA or proteins of the present claims, claims 17-19, 26, 27 and

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33 are drawn to the use of a new, but similar product in an old process of making. It is contended, based on In re Durden, 226 USPQ 359 (Fed. Cir. 1985) and Ex parte Ochiai, 24 USPQ2d 1265 (BPAI, 1992), that the present process is not patentable because the only difference is the new product of Applicant's claimed invention which would have been expected to work in the known process.

The court in Pleuddemann, 15 USPQ 2d 1738 (Fed. Cir. 1990) pointed out that the Durden court determined that the obviousness of a process is to be determined in light of the prior art, each case to be decided on the basis of its own fact situation (page 1741). The Pleuddemann court further pointed out that the claim appealed in Durden was for a method of making a compound. In Pleuddemann, the court found the §103 obviousness of the claims depended on the obviousness of using Appellant's new compounds which constitute the essential limitation of the claims, in light of the prior art. It concluded that the board's hindsight comparison of the functioning of the new compounds with the functioning of the compounds of the prior art was legal error. In upholding appellant's method of use claims it was found that appellant's specification teaching was used as though it were prior art in order to make claims to methods of bonding/priming using his admittedly novel compounds appear to be obvious.

In Ex parte Ochiai the board recognized the Pleuddemann distinction of the method of using claims wherein patentability is linked to patentability of material used and method of making novel material wherein patentability is determined based on inventiveness of process steps. The claims in Ochiai were found to be directed to a process of making and obvious.

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Applicants have discovered a novel DNA sequence encoding a previously unknown protein. As the Examiner states, claims 17-19, 26, 27, and 33 are drawn to the use of a new product, in this case the DNA, which according to the Pleuddemann court the patentability thereof is linked to the patentability of the material used. In short, Applicants submit that these claims directed to the use of the novel DNA in a process for making the protein encoded by the DNA are patentable.

In view of the above, it is submitted that the claims as amended are in condition for allowance. Reconsideration of the rejections and objections is requested.

Should the Examiner believe that a telephonic interview would assist in clarifying any remaining issues or otherwise expedite prosecution, Applicants respectfully invite the Examiner to call the undersigned attorney at the telephone number provided below.

Respectfully submitted,


Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants

Tel: (617) 876-1170
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87 CambridgePark Drive
Cambridge, MA 02140

[ek]5182A.res

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APPENDIX A

6. An isolated DNA sequence encoding a BMP-8 protein comprising the following sequences

a)
GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC CAC (SEQ ID NO: 7);

b)
GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG
GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC
ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)
GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID NO: 11)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

7. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO:13 from nucleotide #8 to #850.

8. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO: 13 from nucleotide #434 through #850.

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9. An isolated DNA comprising the nucleotide sequence of ATCC #75010 encoding BMP-8.

13. A host cell transformed with a DNA of claim 6.

14. A host cell transformed with the DNA of claim 7.

15. A host cell transformed with the DNA of claim 8.

16. A host cell transformed with the DNA of claim 9.

17. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

18. A method comprising the steps of

(a) culturing a cell transformed with a vector comprising

a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

19. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence comprising nucleotide #8 through #850 of SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and

(b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #4 to #142 of (SEQ ID NO:14).

26. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

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27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

28. An isolated DNA sequence encoding a BMP-8 protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:1);
- b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and
- c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a

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molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

33. A method comprising

a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and

b) recovering, isolating and purifying from said culture medium a BMP-8 characterized by the following sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

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iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

35. An isolated DNA comprising the nucleotide sequence of ATCC
#75011 encoding BMP-8.

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By Ellen J. Kapinos
Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|------------|---|---|----------------------|
| Applicant | : | Hewick et al | Group Art Unit: 1814 |
| Serial No. | : | 07/800,364 | Examiner : K. Furman |
| Filed | : | November 26, 1991 | |
| For | : | DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS | |

BOX AF
Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

NOTICE OF APPEAL

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the decision dated April 7, 1994 of the Primary Examiner finally rejecting claims 6, 9, 13, 16-19, 26-33 and 35. Subsequent to Applicants' Request for Reconsideration and Amendment after Final under 37 CFR 1.116, filed herewith, currently pending claims are enclosed herewith as Appendix A to this Appeal.

A Petition for a Three Month Extension of Time and Fee are being filed herewith resetting the date for response from July 7 to October 7, 1994.

Applicants hereby authorize payment of two-hundred and seventy dollars (\$280.00) pursuant to 37 CFR 1.17(a) from Deposit Account No. 07-

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Filed Nov. 26, 1991
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Page 2

1060. Although no additional fees are believed due, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment to Deposit Account No. 07-1060.

Respectfully submitted,



Ellen J. Kapiros
Reg. No. 32,245
Attorney for Applicants
Tel: (617) 876-1170

Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140

SUBMITTED IN TRIPPLICATE

APPENDIX A

6. An isolated DNA sequence encoding a BMP-8 protein comprising the following sequences

a)

GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC
ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC
GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC
CAC (SEQ ID NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG
GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC
ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID
NO: 11)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

7. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO:13 from nucleotide #8 to #850.

8. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO: 13 from nucleotide #434 through #850.

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9. An isolated DNA comprising the nucleotide sequence of ATCC #75010 encoding BMP-8.

13. A host cell transformed with a DNA of claim 6.

14. A host cell transformed with the DNA of claim 7.

15. A host cell transformed with the DNA of claim 8.

16. A host cell transformed with the DNA of claim 9.

17. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

18. A method comprising the steps of

(a) culturing a cell transformed with a vector comprising

a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

19. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence comprising nucleotide #8 through #850 of SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and

(b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #4 to #142 of (SEQ ID NO:14).

26. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

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27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

28. An isolated DNA sequence encoding a BMP-8 protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:1);
- b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and
- c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a

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molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

33. A method comprising

a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and
b) recovering, isolating and purifying from said culture, medium a BMP-8 characterized by the following sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

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iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

35. An isolated DNA comprising the nucleotide sequence of ATCC #75011 encoding BMP-8.

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By Ellen J. Kapinos
Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick et al.

Serial No. : 07/800,364 Examiner : K. Kurman

Filed : November 26, 1991 Art Unit : 1814

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

RESPONSE TO NOTICE AND SUBMISSION OF FORMAL DRAWINGS

Sir:

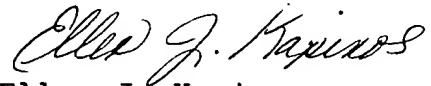
In response to the Notice of Draftsman's Drawing Review accompanying the Office Action mailed February 5, 1993, Applicants hereby submit 3 sheets of formal drawings to replace Figures 1 and 2.

Kindly substitute these formal drawings for the informal drawings currently on file. No new matter is presented by this submission.

USSN 07/800,364
Filed Nov. 26, 1991
GI 5182A
Page 2

Should any fee be due, please charge any such fees associated with this request to Deposit Account 07-1060, and for that purpose, we enclose a duplicate copy of this petition.

Respectfully submitted,



Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617)-876-1170

Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140-2387

NOTICE OF DRAFTSMAN'S PATENT DRAWING REVIEW

The PTO Draftsmen review all originally filed drawings regardless of whether they were designated as informal or formal.

The drawings filed 11/16/92

A. are approved.

B. are objected to under 37 CFR 1.84 for reason(s) checked below. The examiner will require submission of new, corrected drawings at the appropriate time. Corrected drawings must be submitted according to the instructions listed on the back of this Notice.

1. Paper and ink. 37 CFR 1.84(a)

Poor Quality Paper. Must Be White.
Transparent Paper Not Allowed.
Sheet(s) _____

2. Size of Sheet and Margins. 37 CFR 1.84(b)

Acceptable Paper Sizes and Margins

Paper Size

| Margin | 8 1/2 by 14 inches | 8 1/2 by 13 inches | DIN size A4 21 by 29.7 cm. |
|--------|--------------------|--------------------|----------------------------|
| Top | 2 inches | 1 inch | 2.5 cm. |
| Left | 1/4 inch | 1/4 inch | 2.5 cm. |
| Right | 1/4 inch | 1/4 inch | 1.5 cm. |
| Bottom | 1/4 inch | 1/4 inch | 1.0 cm. |

Proper Size Paper Required. All Sheets Must be Same Size.
Sheet(s) _____

 Proper Margins Required.

Sheet(s) _____
 Top Right
 Left Bottom

3. Character of Lines. 37 CFR 1.84(c)

Lines Pale, Rough and Blurred, or Jagged. Fig(s) _____

Solid Black Shading Not Allowed.
Fig(s) _____

 Photographs Not Approved. Comments:

5. Hatching and Shading. 37 CFR 1.84(d)

Shade Lines are Required.
Fig(s) _____

Criss-Cross Hatching Not Allowed.
Fig(s) _____

Double Line Hatching Not Allowed.
Fig(s) _____

Parts in Section Must be Hatched Properly. Fig(s) _____

6. Reference Characters. 37 CFR 1.84(f)

Reference Characters Poor or Rough and Blurred. Fig(s) _____

Minimum 1/8 inch (3.2 mm.) in height is required. Fig(s) _____

Figure Legends Poor or Placed Incorrectly. Fig(s) _____

7. Views. 37 CFR 1.84(i) & (j)

Figures Must be Numbered Separately.

Figures Must Not be Connected
Fig(s) _____

8. Identification of Drawings. 37 CFR 1.84(l)

Extraneous Matter or Copy Machine Marks Not Allowed. Fig(s) _____

 Changes Not Completed from Prior PTO-948 dated _____

Telephone inquiries concerning this review should be directed to the Chief Draftsman at telephone number (703) 557-6404.

2/20/92

Reviewing Draftsman

Date

FIGURE 1

52 Standard



FIGURE 2

(1) GAATTCC GAG CCC CAT TGG AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC CCG GCT
 Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala
 (1)

GGG GAG GCG GTC ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG CCC AGC ATC CAC
 Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His
 (20)

CTG CTC AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG GTG GTC CAG GAG CAG TCC
 Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser
 (40)

AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT CTT CAG ACG CTC CGA GCT GGA GAC
 Asn Arg Glu Ser Asp Leu Phe Leu Asp Leu Gln Thr Leu Arg Ala Gly Asp
 (60)

GAG GGC TGG CTG GTG CTG GAT GTC ACA GCA GCC AGT GAC TGC TGG TTG CTG AAG
 Glu Gly Tyr Leu Val Asp Val Thr Ala Ala Ser Asp Cyc Trp Leu Leu Lys
 (80)

CGT CAC AAG GAC CTG GGA CTC CGC CTC TAT GTG GAG ACT GAG GAT GGG CAC AGC
 Arg His Lys Asp Leu Gly Lue Arg Leu Tyr Val Glu Thr Glu Asp Gly His Ser
 (90)

GTG GAT CCT GGC CTG GCC GGC CTG GGT CAA CGG GCC CCA CGC TCC CAA CAG
 Val Asp Pro Gly Leu Ala Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln
 (110)

CCT TTG GTC ACT TTC TTC AGG GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG
 Pro Phe Val Val Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg
 (130)

(450) GCA GTG AGG CCA CTG AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG CCG CAG
 Ala Val Arg Pro Leu Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln
 (143)

(150)

(160)

FIGURE 2A

GCC AAC CGA CTC CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC CAC GGC CGG CAG
Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly Arg Gln
(170)

GTC TGC CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG GAC CTT GGC TGG CTG GAC
Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp
(180)

TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAG GGG GAG TGC TCC
Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser
(200)

TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG
Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu
(220)

GTC CAC CTG ATG AAG CCA AAC GCA GTC CCC AAG GCG TGC TGT GCA CCC ACC AAG
Val His Leu Met Lys Pro Asn Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys
(240)

CTG AGC GCC ACC TCT GTG CTC TAC TAT GAC AGC AGC AAC AAC GTC ATC CTG CGC
Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg
(260)

AAG CAC CGC AAC ATG GTG GTC AAG GCC TGC GGC TGC CAC TGAGTCAGCCGCCAGC
Lys His Arg Asn Met Val Val Lys Ala Cys Gly Cys His
(280)

CCTACTGCAGGCCACCCCTTCTCATCTGGATCGGGCCCTGGAGGGCAGAAAACCCCTAAATGCTGTCA
(843)

CTCAAGCAGGTGTCAGGGCCCTCACTCTGGTGCCTACTCTGGTGCCTACTCTGGCTTCAGGGTTCTGGAAATT
(270)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

Title : BONE AND CARTILAGE INDUCTIVE PROTEINS

*I hereby certify that this correspondence is being deposited with the
 United States Postal Service as ~~first class~~ mail in an envelope addressed
 to Honorable Commissioner of Patents and Trademarks, Washington,
 D.C. 20231 on October 5, 1994.*

"Express Mail" number RB793967900US BY: *Ellen J. Kapines*

Hon. Commissioner of Patents
 and Trademarks
 Washington, D.C. 20231

STATEMENT PURSUANT TO 37 CFR 1.825(a)

Pursuant to Part III of the Final Office Action dated April 7, 1994 received from the Patent and Trademark Office stating that the "Sequence Listing" does not comply with the requirements of §§1.821 through 1.825, a substitute and amended copy of the computer readable form of the Sequence listing which was duly submitted with the application as filed, is provided herewith.

Please substitute this amended Sequence Listing for the originally-filed Sequence Listing. The Sequence Listing and enclosed diskette now contain SEQ ID NOS:1-15.

This affirms that to the best of my knowledge and belief, these amendments present no substantive changes to the Sequence Listing and the computer readable copy of said Sequence Listing as originally filed. No new matter has been added.

Respectfully submitted,

October 4, 1994
 Date

Ellen J. Kapines
 Ellen J. Kapines
 Reg. No. 32,245
 Legal Affairs
 Genetics Institute, Inc.
 87 CambridgePark Drive
 Cambridge, MA 02140
 (617) 876-1170

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick, et al.

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I hereby certify that this correspondence is being deposited with the
United States Postal Service as ~~first class~~ ^{EXPRESS} mail in an envelope addressed
to Honorable Commissioner of Patents and Trademarks, Washington,
D.C. 20231 on October 5, 1994.

"Express Mail" number RB793967900US BY: Ellen J. Kapinos

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

STATEMENT PURSUANT TO 37 CFR 1.825(b)

Sir:

A substitute and amended copy of the computer readable form of the Sequence Listing which was duly submitted with the application, as filed, is provided herewith. This affirms that to the best of my knowledge and belief, the content of the substitute Sequence Listing and the computer readable copy of said Sequence Listing provided herewith are the same.

Respectfully submitted,

October 4, 1994
Date

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Legal Affairs
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140
(617) 876-1170

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Hewick, Rodney M.
Wang, Jack H.
Wozney, John M.
Celeste, Anthony J.

(ii) TITLE OF INVENTION: Bone and Cartilage Inductive Proteins

(iii) NUMBER OF SEQUENCES: 15

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Legal Affairs, Genetics Institute, Inc.
(B) STREET: 87 CambridgePark Drive
(C) CITY: Cambridge
(D) STATE: MA
(E) COUNTRY: USA
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/800,364
(B) FILING DATE: 26-NOV-1991
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Kapinos, Ellen J.
(B) REGISTRATION NUMBER: 32,245
(C) REFERENCE/DOCKET NUMBER: GI 5182A

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617-876-1170
(B) TELEFAX: 617-876-5851

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp
 1 5 10 15

Val Ile Ala Pro Gln Gly Tyr
 20

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile
 1 5 10 15

Leu Arg

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ala Cys Cys Ala Pro Thr Lys
1 5

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Thr Asn Glu Leu Pro Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp
1 5 10 15

Val His Gly Ser His Gly Arg

20

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 80 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
 (A) ORGANISM: *Bos taurus*

(vii) IMMEDIATE SOURCE:
 (B) CLONE: acc30

(viii) POSITION IN GENOME:
 (C) UNITS: bp

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 25..57

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GGATCCGCGT GCTGTGCTCC GACC AAG CTG AGC GCC ACC TCC GTG CTC TAC 51
 Lys Leu Ser Ala Thr Ser Val Leu Tyr
 1 5

TAC GAC AGCAGCAACA ATGTAATTCT AGA 80
 Tyr Asp
 10

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 11 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp
 1 5 10

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 199 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: *Bos taurus*

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Bovine genomic
- (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:

(C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 30..199

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..29

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 30..179

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TGCCCGCTGC CCCCTCCCGC CCCCGCCAG GTG CAC CTG CTG AAG CCG CAC GCG 53
 Val His Leu Leu Lys Pro His Ala
 1 5

GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG 101
 Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val
 10 15 20

CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC 149
 Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn
 25 30 35 40

ATG GTG GTC CGC GCC TGC GGC TGC CAC TGAGGCCCA ACTCCACCGG 196
 Met Val Val Arg Ala Cys Gly Cys His
 45 50

CAG 199

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Val His Leu Leu Lys Pro His Ala Val Pro Lys Ala Cys Cys Ala Pro
 1 5 10 15

Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn
 20 25 30

Val Ile Leu Arg Lys His Arg Asn Met Val Val Arg Ala Cys Gly Cys
 35 40 45

His

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 172 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Bos taurus*

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Bovine genomic
- (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 51..161

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..50

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 162..172

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 51..161

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

| | | |
|---|-----|----|
| GGGGTGGGAG GGCACGTGGA TGGGACTCAC CTTCTCCAC TACCCCCAG GAC TGG | 56 | |
| Asp Trp | | |
| 1 | | |
| | | |
| GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC | 104 | |
| Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys | | |
| 5 | 10 | 15 |
| | | |
| TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG | 152 | |
| Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu | | |
| 20 | 25 | 30 |
| | | |
| CAG TCC CTG GTCAGTACCT C | 172 | |
| Gln Ser Leu | | |
| 35 | | |

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

| | | | |
|---|----|----|----|
| Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly | | | |
| 1 | 5 | 10 | 15 |
| | | | |
| Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala | | | |
| 20 | 25 | 30 | |
| | | | |
| Ile Leu Gln Ser Leu | | | |
| 35 | | | |

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 119 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
 (A) ORGANISM: *Bos taurus*

(vii) IMMEDIATE SOURCE:
 (A) LIBRARY: Bovine genomic
 (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:
 (C) UNITS: bp

(ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION: 20..99

(ix) FEATURE:
 (A) NAME/KEY: intron
 (B) LOCATION: 1..19

(ix) FEATURE:
 (A) NAME/KEY: intron
 (B) LOCATION: 100..119

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 22..99

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CCCTTGCCTG TCCCCGCAGA C GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG 51
 Asp Val His Gly Ser His Gly Arg Gln Val
 1 5 10

TGC CGT CGG CAC GAG CTG TAC GTG AGC TTC CAG GAC CTG GGC TGG CTG 99
 Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu
 15 20 25

GTGAGTTCCG ACTCTCCTTT 119

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 26 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His Glu Leu
 1 5 10 15

Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu
 20 25

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1003 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Homo sapiens*
- (F) TISSUE TYPE: Human Heart

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Human heart cDNA library stratagene catalog
#936208
- (B) CLONE: hH38

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 8..850

(ix) FEATURE:

- (A) NAME/KEY: mat_peptide
- (B) LOCATION: 427..843

(ix) FEATURE:

- (A) NAME/KEY: mRNA
- (B) LOCATION: 1..997

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAATTCC GAG CCC CAT TGG AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC
 Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile
 -139 -135 -130

| | |
|---|-----|
| CCG GCT GGG GAG GCG GTC ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val -125 -120 -115 -110 | 97 |
| CCC AGC ATC CAC CTG CTC AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG Pro Ser Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln -105 -100 -95 | 145 |
| GTG GTC CAG GAG CAG TCC AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT Val Val Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp -90 -85 -80 | 193 |
| CTT CAG ACG CTC CGA GCT GGA GAC GAG GGC TGG CTG GTG CTG GAT GTC Leu Gln Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val -75 -70 -65 | 241 |
| ACA GCA GCC AGT GAC TGC TGG TTG CTG AAG CGT CAC AAG GAC CTG GGA Thr Ala Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly -60 -55 -50 | 289 |
| CTC CGC CTC TAT GTG GAG ACT GAG GAT GGG CAC AGC GTG GAT CCT GGC Leu Arg Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly -45 -40 -35 -30 | 337 |
| CTG GCC GGC CTG CTG GGT CAA CGG GCC CCA CGC TCC CAA CAG CCT TTC Leu Ala Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe -25 -20 -15 | 385 |
| GTG GTC ACT TTC TTC AGG GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG Val Val Thr Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg -10 -5 1 | 433 |
| GCA GTG AGG CCA CTG AGG AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG Ala Val Arg Pro Leu Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu 5 10 15 | 481 |
| CCG CAG GCC AAC CGA CTC CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC Pro Gln Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser 20 25 30 35 | 529 |
| CAC GGC CGG CAG GTC TGC CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG His Gly Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln 40 45 50 | 577 |
| GAC CTT GGC TGG CTG GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala 55 60 65 | 625 |
| TAT TAC TGT GAG GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn 70 75 80 | 673 |

| | |
|--|------|
| GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG GTG CAC CTG ATG AAG CCA Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro | 721 |
| 85 90 95 | |
| AAC GCA GTC CCC AAG GCG TGC TGT GCA CCC ACC AAG CTG AGC GCC ACC Asn Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr | 769 |
| 100 105 110 115 | |
| TCT GTG CTC TAC TAT GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His | 817 |
| 120 125 130 | |
| CGC AAC ATG GTG GTC AAG GCC TGC GGC TGC CAC TGAGTCAGCC CGCCCAGCCC Arg Asn Met Val Val Lys Ala Cys Gly Cys His | 870 |
| 135 140 | |
| TACTGCAGCC ACCCTTCTCA TCTGGATCGG GCCCTGCAGA GGCAGAAAAC CCTTAAATGC | 930 |
| TGTCACAGCT CAAGCAGGAG TGTCAGGGC CCTCACTCTC GGTGCCTACT TCCTGTCAGG | 990 |
| CTTCTGGGAA TTC | 1003 |

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 281 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala
-139 -135 -130 -125

Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser
-120 -115 -110

Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val
-105 -100 -95

Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln
-90 -85 -80

Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val Thr Ala
-75 -70 -65 -60

Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly Leu Arg
-55 -50 -45

Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly Leu Ala
 -40 -35 -30

Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe Val Val
 -25 -20 -15

Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg Ala Val
 -10 -5 1 5

Arg Pro Leu Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln
 10 15 20

Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly
 25 30 35

Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu
 40 45 50

Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr
 55 60 65

Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr
 70 75 80 85

Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro Asn Ala
 90 95 100

Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val
 105 110 115

Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn
 120 125 130

Met Val Val Lys Ala Cys Gly Cys His
 135 140

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 112 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His Glu Leu
1 5 10 15

Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Leu Leu Val Ile Ala Pro
20 25 30

Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu
35 40 45

Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val
50 55 60

His Leu Leu Lys Pro His Ala Val Pro Lys Ala Cys Cys Ala Pro Thr
65 70 75 80

Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val
85 90 95

Ile Leu Arg Lys His Arg Asn Met Val Val Arg Ala Cys Gly Cys His
100 105 110

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Rod Hewick, et al.

Serial No.: 07/800,364

Examiner: K. Furman

Filed : November 26, 1991

Art Unit: 1814

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 13, 1994

Hon. Commissioner
 of Patents and Trademarks
 Washington, D.C. 20231
 ATTN: Donna Chapman, Supervisor

| | |
|---|---|
| Certificate of Facsimile Transmission | |
| I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below. | |
| <u>Diana Gentile</u> | Type or print name of person signing certificate. |
| <u>Diana Gentile</u> | Signature |
| 1/13/94 | |
| Date | |

LETTER

This is in response to the telephone conference with Ms. Donna Chapman January 11, 1994. Ms. Chapman instructed Applicants to send or fax a copy of the amendment filed August 4, 1993. Although this amendment was received by the Patent and Trademark Office as evidenced by the enclosed return postcard bearing an August 4, 1993 mailroom stamp, a Notice of Abandonment was received September 17, 1993.

Ms. Chapman indicated during the January 11 telephone conference that extension and other fees relating to this application had in fact been charged to Applicants' Deposit Account No. 07-1060.

The following documents are faxed herewith to (703) 305-3014.

1. Mail room receipt postcard bearing August 4, 1993 stamp
2. Transmittal Letter (1 page)
3. Extension of Time (1 page)
4. Information Disclosure Statement (2 pages)
5. Form PTO-1449 (2 pages)
6. Amendment with Appendix A (20 pages)
7. Deposit Declaration (2 pages)

A copy of these documents as well as ten references listed on PTO-1449 and PCT/US91/03388 are being hand delivered to Ms. Chapman within a few days.

In view of the above, it is respectfully submitted that the Notice of Abandonment be withdrawn and the response of August 4, 1993 be considered by the Examiner.

No fee is believed due. However, if any fee should be due, authorization is hereby given to charge it to our Deposit Account No. 07-1060. Two copies of this sheet are enclosed.

Respectfully submitted,

January 13, 1994
Date

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants

Legal Affairs
GENETICS INSTITUTE, INC.
87 CambridgePark Drive
Cambridge, Massachusetts 02140

PATENT

Serial No. 07/800,364 Doc. No. 61-51824 Atty/Sec EK/06 Date 1/17/94
Inventor Rod Henick, et al.

Title Bone and Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

| | |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> Claim, <input type="checkbox"/> Abstract | <input checked="" type="checkbox"/> <u>20</u> pp. Amendment/ ^{1/17/94} <u>copy</u> OA dtd <u>2-5-93</u> |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input type="checkbox"/> <u>1</u> pp. Response: OA dtd _____ |
| <input type="checkbox"/> pp. Verified Statement (Small Entity) | <input checked="" type="checkbox"/> <u>1</u> pp. Transmittal Letter ^(copy) |
| <input type="checkbox"/> shts. Informal Drawings | <input type="checkbox"/> Issue Fee |
| <input type="checkbox"/> shts. Formal Drawings | <input type="checkbox"/> Notice of Appeal & Fee |
| <input type="checkbox"/> pp. Assignment | <input type="checkbox"/> Check # _____ for \$ _____ |
| <input type="checkbox"/> pp. Preliminary Amendment | <input checked="" type="checkbox"/> <u>Letter</u> |
| <input checked="" type="checkbox"/> <u>1</u> pp. Extension of Time ^(copy) | <input checked="" type="checkbox"/> <u>Deposit Declaration -copy</u> |
| <input checked="" type="checkbox"/> <u>2</u> pp. ^(copy) Information Disclosure Statement with PTO-1499 and <u>16</u> references ^(copy) | <input checked="" type="checkbox"/> <u>Copy of PCT/US91/03386</u> |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

*Confirmation copy to be
Hand delivered by Betty Byrd, Inc.*

Respectfully,
Genetics Institute, Inc.

PATENT

Serial No. 07/800,364 Doc. No. 61-51824 Atty/Sec EK/06 Date 1/17/94
Inventor Rod Henick, et al.

Title Bone and Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

| | |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> Claim, <input type="checkbox"/> Abstract | <input checked="" type="checkbox"/> <u>20</u> pp. Amendment/ ^{1/17/94} <u>copy</u> OA dtd <u>2-5-93</u> |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input type="checkbox"/> <u>1</u> pp. Response: OA dtd _____ |
| <input type="checkbox"/> pp. Verified Statement (Small Entity) | <input checked="" type="checkbox"/> <u>1</u> pp. Transmittal Letter ^(copy) |
| <input type="checkbox"/> shts. Informal Drawings | <input checked="" type="checkbox"/> Issue Fee |
| <input type="checkbox"/> shts. Formal Drawings | <input type="checkbox"/> Notice of Appeal & Fee |
| <input type="checkbox"/> pp. Assignment | <input type="checkbox"/> Check # _____ for \$ _____ |
| <input type="checkbox"/> pp. Preliminary Amendment | <input checked="" type="checkbox"/> <u>Letter</u> |
| <input checked="" type="checkbox"/> <u>1</u> pp. Extension of Time ^(copy) | <input checked="" type="checkbox"/> <u>Deposit Declaration -copy</u> |
| <input checked="" type="checkbox"/> <u>2</u> pp. ^(copy) Information Disclosure Statement with PTO-1499 and <u>16</u> references ^(copy) | <input checked="" type="checkbox"/> <u>Copy of PCT/US91/03386</u> |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

*Confirmation copy to be
Hand delivered by Betty Byrd, Inc.*

Respectfully,
Genetics Institute, Inc.

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20591

DOCKET NO.: GI 5182A

(15)

SERIAL NO.: 07/800,364
FILED: November 26, 1991
GROUP ART UNIT: 1814

SIR:

In re application of: Rod Hewick et al.

Entitled: BONE AND CARTILAGE INDUCTIVE PROTEINS

Transmitted herewith is an Amendment in the above-identified application. The following checked items are applicable:

A Petition for Extension of Time for 3 months is hereby made, under §1.136(a) and fee is calculated herein;

Other: Declaration of Deposit Requirements and enclosures
Information Disclosure Statement with 10 references attached.

| Claims after amendment | Minus Prior PAID claims | Equals present extra claims | RATE | FEE |
|---|-------------------------|-----------------------------|---------------------------|----------|
| Independent 8 | - 13 | = | x \$74.00 = | \$.00 |
| Total 21 | - 25 | = | x \$22.00 = | \$.00 |
| [] Multiple Dependent Claims (1st presentation) | | | +\$230.00 | \$.00 |
| [XX] Information Disclosure fee pursuant to revised §1.97 & §1.98 | | | +\$200.00 | \$200.00 |
| | | | SUBTOTAL FEE | \$.00 |
| [X] Petition for Extension of time fee pursuant to §1.17 | | | extension within 3 months | \$840.00 |
| | | | TOTAL ADDITIONAL FEE | \$840.00 |

The fee has been calculated above; The Commissioner is hereby authorized to charge payment of \$840.00 under §1.16 associated with this communication or credit any overpayment to Deposit Account No. 07-1060.

[] No additional fee is believed due.

CERTIFICATE OF MAILING RB 793966844 US
Date of Deposit August 4, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service Via Express Mail Post Office to "Addressee" service under 37 C.F.R. 1.10 on date indicated above and addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Ellen J. Kapiro

Ellen J. Kapiro
Attorney of Record: Ellen J. Kapiro
Registration No. 32,245

Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140

SUBMITTED IN TRIPPLICATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick et al.

Serial No. : 07/800,364

Examiner : K. Kurman

Filed : November 26, 1991

Art Unit : 1814

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

RB 793966844 US
"Express Mail" mailing label number:Date of Deposit: August 4, 1993

August 2, 1993

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231,

Ellen J. Kapinos

PETITION AND FEE FOR EXTENSION OF TIME UNDER 37 CFR 1.136

We hereby request an extension of time for response of three (3) month/s pursuant to 37 CFR 1.136(a) in which to respond to the Office Action mailed February 5, 1993. This extension resets the time for response from May 5, 1993 to August 5, 1993.

We authorize the charging of Eight Hundred and Forty (\$840.00) and any additional fees and crediting of overpayment to our Deposit Account 07-1060, and for this purpose, we enclose a duplicate copy of this petition.

Respectfully submitted,

Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617)-876-1170

August 3, 1993
Date

Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140-2387

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick et al.

Serial No. : 07/800,364

Examiner : K. Furman

Filed : November 26, 1991

Art Unit : 1814

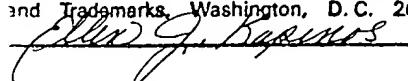
For : BONE AND CARTILAGE INDUCTIVE PROTEINS

August 2, 1993

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

"Express Mail" mailing label number, RB193966844 US
Date of Deposit: August 4, 1993

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.



Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the provisions of 37 C.F.R. §§ 1.56 and 1.97, 1.98(d) the publications and/or patents listed on the attached form PTO-1449 are cited for consideration by the Examiner in connection with the examination of the above-identified patent application. It is understood that the references need not be provided herewith as they have been previously submitted to the Office in the prior parent application. Those references which are marked by an asterisk have been provided herewith as they were not cited in the parent and comprise the most recent relevant art of which applicant is aware.

In accordance with the provisions of 37 C.F.R. §1.97, this statement is being filed (CHECK ONE):

- (1) within three (3) months of the Filing Date or before the mailing date of the First Office Action on the merits; or
- (2) after the period defined in (1) but before the mailing date of a Final Rejection or Notice of Allowance, and the requisite Certification or fee under Rule 1.17(p), namely \$200.00, is included herein; or
- (3) after the mailing date of a Final Rejection or Notice of Allowance but before the payment of the Issue Fee, and the requisite Certification, petition, and petition fee are included herein.

It is respectfully requested that each of the documents shown on the attached form PTO-1449 be made of record in this application.

Early examination and allowance of the present application are respectfully solicited.

Should any fee associated with the submission of this paper not be attached hereto as a check, the Commissioner is authorized to charge the missing fee to our Deposit Account, No. 07-1060. Any overpayments should be credited to said Deposit Account.

Respectfully submitted,



Legal Affairs
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, Massachusetts 02140

Ellen J. Kepinos
Reg. No. 32,245
Attorney for Applicants
(617)-876-1170

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Hewick et al

Group Art Unit: 1814

Serial No.: 07/800,364

Examiner : K. Furman

Filed : November 26, 1991

For : DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS

August 4, 1993

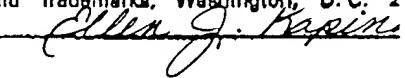
Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

RB 793966844 US

"Express Mail" mailing label number.

Date of Deposit August 4, 19

I hereby certify that this paper or fee is
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"Express Mail Post Office to Addressee" e
under 37 C.F.R. 10 on the date indicated
and is addressed to the Commissioner of P
and Trademarks, Washington, D.C. 20231



Sir:

This is in response to the Office Action mailed February 5, 1993. A Request for a Three Month Extension and Fee accompanies this amendment. The Extension resets the time for response from May 5, to April 5, 1993.

Please amend the application as follows:

In the Specification:

Change the title to -- DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS --

Page 1, line 34, delete "Figure 2".

Page 2, insert the numeral --2-- at the top center of the page.

Page 2, lines 2-3, delete "#143 (Ala)- #281 (His) of Figure 2" and insert -- #4 (Ala) - #142 (His) of SEQ ID NO: 14, therefor.

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991

Page 2, line 4, delete "Figure 2" and insert -- SEQ ID NO: 14-- therefor.

Page 2, line 35, delete "#1 through #843" and insert --#8 through #850--, therefor.

Page 3, line 1 delete "Figure 2".

Page 4, lines 4-5 delete "#143 through #281 of Figure 2" and insert --#4 through #142--, therefor.

Page 4, line 15, delete "#1 to #843 in Figure 2" and insert -- #8 to #850 of SEQ ID NO: 13--, therefor.

Page 4, lines 17 and 22, delete " #143 to #281 of Figure 2" and insert -- #4 to # 142 of SEQ ID NO: 14 -- , therefor.

Page 4, line 23 delete "#143" and insert --#4-- , therefor.

Page 6, line 24 delete "Figure 2".

Page 8, line 1, delete "#143 through 281 of Figure 2" and insert -- #4 through #142 of SEQ ID NO: 14 --, therefor.

Page 8, lines 7-8, delete "#143 (Ala) - #281 (His) of Figure 2" and insert --#4 (Ala) - #142 (His) of SEQ ID NO: 14--, therefor.

Page 8, lines 9 and 13, delete "Figure 2" and insert --SEQ ID NO:14 --, therefor.

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Group Art Unit 1814
Filed: November 26, 1991

Page 11, line 20, delete "#143 through #281 of Figure 2" and insert -- #4 through #142 of SEQ ID NO: 14 --, therefor.

Page 11, line 23, delete "Figure 2" and insert --SEQ ID NO:14--, therefor.

Page 11, lines 27-28, delete "#143 (Ala) - #281 (His) of Figure 2" and insert -- #4 (Ala) - #142 (His) of SEQ ID NO: 14--, therefor.

Page 11, line 29, delete "Figure 2" and insert -- SEQ ID NO: 14--.

Page 29, line 22, delete "fragmnet" and insert --fragment--, therefor.

Page 32, lines 6-7 delete "(SEQ ID NO:13)".

Page 32, line 7, after "Table 4" insert -- which corresponds to the sequence of SEQ ID NO:14 from amino acid position number 31 through position 142, wherein Met at position 97 is replaced with Leu, Asn at position 100 is replaced with His, and Lys at position 137 is replaced with Arg. --

Page 35, line 33, delete "Figure represent" and insert --SEQ ID NO:14 represents--, therefor.

Page 36, line 7, delete "#143 - #281 of Figure 2" and insert -- #4 - #142 of SEQ ID NO: 14--, therefor.

Page 36, line 9, delete "Figure 2" and insert --SEQ ID NO:14--, therefor.

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Group Art Unit 1814
Filed: November 26, 1991

Page 36, line 11, delete "Figure 2" and insert --SEQ ID NO:13--, therefor.

Page 37, line 32, delete "#1 to #846 of Figure 2" and insert -- #8 to #853 of SEQ ID NO:13--, therefor.

In the Claims:

6. (once amended) An isolated DNA sequence [encoding a BMP-8 protein said DNA sequence] comprising [at least one of] the following sequences

a)

GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC CAC (SEQ ID NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG
TGC CGTCGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID NO: 11).

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Group Art Unit 1814
Filed: November 26, 1991

[d) the nucleotide sequence comprising nucleotide #1 through #843 of Figure 2 (SEQ ID NO:13); and

e) the nucleotide sequence comprising nucleotide #430 through #843 of Figure 2 (SEQ ID NO:13).]

7. (twice amended) An isolated DNA sequence comprising the nucleotide sequence set forth in [Figure 2 ()SEQ ID NO:13()] from nucleotide #[1]8 to #[843]850.

8. (twice amended) An isolated DNA sequence comprising the nucleotide sequence set forth in [Figure 2 ()SEQ ID NO: 13()] from nucleotide #[430]434 through #[843]850.

9. (once amended) An isolated DNA comprising [T]the DNA sequence of ATCC #75010 [encoding BMP-8].

17. (once amended) A method [for producing a BMP-8 protein said method] comprising the steps of:

(a) culturing a cell transformed with a vector comprising [having] a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture

medium a protein encoded by said DNA sequence [characterized by the ability to induce cartilage and/or bone formation].

18. (once amended) A method [for producing a purified BMP-8 protein said method] comprising the steps of

- (a) culturing a cell transformed with a vector comprising [having] a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence [characterized by the ability to induce cartilage and/or bone formation].

19. (twice amended) A method [for producing a purified BMP-8 protein said method] comprising the steps of:

- (a) culturing a cell transformed with a vector comprising [having] a DNA sequence comprising nucleotide #[1]8 through #[843]850 of [Figure 2] SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and
- (b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #[143]4 to #[281]142 of [Figure 2] (SEQ ID NO:14).

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Add new claims:

26. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

28. A DNA sequence encoding a protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

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b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3).

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

33. A method comprising

a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and

b) recovering, isolating and purifying from said culture medium a BMP-8 characterized by the following sequences

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Filed: November 26, 1991

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-
Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:
1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

34. A method for isolating a DNA sequence comprising

a) designing nucleotide probes based on the following amino acid sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-
Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:
1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2);

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

b) screening a selected library with said probes; and isolating said DNA sequence from said library said DNA encoding a protein comprising the sequences set forth in i) through iii).

USSN 07/800,364
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35. An isolated DNA sequence comprising the nucleotide sequence of ATCC #75011.

REMARKS

Reconsideration of the application and entry of the amendments is requested.

The following documents accompany this response:

1. Appendix A - Claims
2. Information Disclosure Statement, PTO Form 1449, required fee and references.
3. Petition for Extension of Time and Required Fee
4. Deposit Declaration

The Draftsman's Drawing Review has been noted. In accordance with 37 CFR 1.85, Applicants will submit corrected formal drawings upon notification of allowance of claims in the present application.

Applicants have requested a certified copy of PCT/US91/03388 for which priority is claimed under 35 USC 119. A copy of PCT/US91/03388 is enclosed and the certified copy will be forwarded as soon as it is received.

Minor amendments have been made to the specification. The title has been changed to reflect the nature of the claimed invention. Claims 1-5, 10-12 and 20-25 have been deleted. Claims

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Group Art Unit 1814
Filed: November 26, 1991

6-9 and 17-19 have been amended. New claims 26-35 have been added. Basis for the new claims appears throughout the specification for example, claims 26, 27 and 33: page 10, line 30 to page 12, line 29, page 36, line 25 to page 39, line 20; claim 28, page 3, lines 10-22; claims 29 and 30, page 8, lines 28-33; claim 31, page 12, line 30 to page 13, line 10; claim 32, page 10, lines 4-18; claim 34, page 8, line 34 to page 9, line 4 and page 34, line 28 to page 35, line 8; and claim 35, page 28, line 24 to page 35, line 4. For convenience the claims as amended appear in Appendix A.

An Information Disclosure Statement, Form 1449 and authorization to charge the \$200.00 fee to Deposit Account No. 07-1060 accompanies this document. Copies of listed references which have not been previously submitted in parent applications are submitted herewith.

The objections and rejections are addressed below in order of their appearance in the office action.

Restriction Requirement

Applicants hereby confirm the election of Group II, claims 6-9 and 13-19. It is Applicants understanding that an election of species is not necessary because all species were searched and examined on the merits. Claims 1-5, 10-12 and 20-25 stand withdrawn from further consideration in this Application. Applicants hereby preserve their rights to pursue the subject matter contained in these withdrawn claims in one or more divisional applications filed pursuant to 35 U.S.C. 121. It is believed that the inventorship remains the same despite the withdrawal of non-elected claims.

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991

Rejections Based on 35 USC §112

The specification is objected to as failing to provide an adequate written description of the invention because of an error in referencing a SEQ ID for the bovine BMP-8 sequence in the last line of page 32. The specification has been amended, as suggested by the Examiner, indicating that the bovine BMP-8 sequence of Table 4 "corresponds to the sequence of SEQ ID NO:14 from amino acid position number 31 through position 142 wherein Met at position 97 is replaced with Leu, Asn at position 100 is replaced with His and Lys at position 137 is replaced with Arg."

The written description is also considered inadequate because where a SEQ ID NO: follows a reference to a Figure it is not clear whether the sequence of the SEQ ID is the equivalent of the entire Figure or the range of positions in the Figure because the position numbers in the Figures differ from the numbers in the SEQ ID. The specification has been amended to specifically reference the SEQ ID and position numbers for the SEQ ID. Reference to Figure 2 has been deleted. The specification as amended is considered to provide an adequate written description.

Claims 6, 13 and 17 are rejected as the disclosure is enabling only for claims limited to where the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2. It is submitted that the claims as amended are enabled by the disclosure. Claim 6 as amended and claims 13 and 17 dependent thereon are directed to a DNA comprising three sequences [a), b) and c)] which form part of the nucleotide sequence encoding BMP-8.

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991

Claims 17 and 18 are rejected as the disclosure is enabling only for claims limited wherein the protein recovered in step (b) is the one encoded by the coding regions of the DNA sequence of step (a) in both claims 17 and 18 and in claim 17 wherein the sequence is either that set forth in d) or e) or DNAs which encode the same protein(s) encoded by the DNAs of species d) or e). The claims have been amended to limit the protein recovered in step (b) to proteins encoded by the coding regions of the DNA of step (a). As discussed above, claim 6 (upon which claim 17 depends) has been amended to set forth three nucleotide sequences [a), b) and c)] which comprise part of the DNA sequence encoding BMP-8. It is therefore submitted that the claims as amended are enabled by the disclosure.

The specification is objected to as failing to provide an enabling disclosure for the claimed invention because the sequence of the DNA encoding BMP-8 of ATCC #75010 is not elsewhere disclosed and this DNA is claimed. The Examiner contends that the specification does not provide a repeatable method for obtaining ATCC #75010. Applicants submit that the description set forth on page 33, line 26 through page 34, line 27 provides a repeatable method for obtaining the DNA encoding BMP-8 of ATCC #75010. As suggested by the Examiner, a Declaration by the undersigned Attorney of record is submitted herewith to satisfy the deposit requirements. The Declaration states that ATCC #75010 and #75011 have been deposited under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public will be irrevocably removed upon the granting of a patent. It is therefore considered that the specification provides an enabling disclosure for claims 9 and 18.

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991

Claims 6-8, 13-15 and 19 are rejected as being indefinite because it is not clear whether the sequence of the SEQ ID NO: is the equivalent of the entire sequence of the Figure or the equivalent of the sequence corresponding to the range of positions in the Figure. Furthermore, it is noted by the Examiner that the position numbers of the Figures do not correspond with the SEQ ID. As recommended by the Examiner the claims have been amended to refer only to the SEQ ID and positions thereof. Claim 19 has been amended to reference a SEQ ID.

Rejections Based on 35 USC §101

Claims 6, 9, 13 and 16 are rejected for being directed to non-statutory subject matter. It is contended that the DNAs of species a), b) and c) of claim 6 and 9 and the host cells have the same characteristics and utility as that found in nature. The claims as amended are directed to isolated DNA sequences and are therefore considered to be distinguished from that found in nature.

In view of the above, it is submitted that the claims as amended are in condition for allowance. Reconsideration of the rejections and objections is requested.

Respectfully submitted,

Date August 4, 1993

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
Tel: (617) 876-1170

Genetics Institute, Inc.
87 Cambridge Park Drive
Cambridge, MA 02140

[legal.patent]5182Aamend

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991

APPENDIX A

6. An isolated DNA sequence comprising the following sequences

a)

GTC CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC ACC
AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC
CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC CAC (SEQ ID
NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GCC TAC TCA GCC TAT TAC TGT GAA GGG GAG
TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG
CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID NO:
11).

7. An isolated DNA sequence comprising the nucleotide sequence set
forth in SEQ ID NO:13 from nucleotide #8 to #850.

8. An isolated DNA sequence comprising the nucleotide sequence set
forth in SEQ ID NO: 13 from nucleotide #434 through #850.

9. An isolated DNA comprising the DNA sequence of ATCC #75010.

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Group Art Unit 1814
Filed: November 26, 1991

13. A host cell transformed with a DNA of claim 6.

14. A host cell transformed with the DNA of claim 7.

15. A host cell transformed with the DNA of claim 8.

16. A host cell transformed with the DNA of claim 9.

17. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

18. A method comprising the steps of

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 9 in operative association with a n expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991

19. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence comprising nucleotide #8 through #850 of SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and
- (b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #4 to #142 of (SEQ ID NO:14).

26. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

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Filed: November 26, 1991

28. A DNA sequence encoding a protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);
- b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and
- c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3).

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991

33. A method comprising

a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and

b) recovering, isolating and purifying from said culture medium a BMP-8 characterized by the following sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

34. A method for isolating a DNA sequence comprising

a) designing nucleotide probes based on the following amino acid sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

USSN 07/800,364
Group Art Unit 1814
Filed: November 26, 1991

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2);

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

b) screening a selected library with said probes; and isolating said DNA sequence from said library said DNA encoding a protein comprising the sequences set forth in i) through iii).

35. An isolated DNA sequence comprising the nucleotide sequence of ATCC #75011.

GI 5182A
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rod Hewick et al.

Group Art Unit : 1814

Serial No.: 07/800,364

Examiner : K. Furman

Filed : November 26, 1991

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

August 2, 1993

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

RB 793966844US

"Express Mail" mailing label number:
Date of Deposit: August 4, 1993

I hereby certify that this paper or fee is being
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and is addressed to the Commissioner of Patents
and Trademarks, Washington, D.C. 20231.

Ellen J. Kapinos

DECLARATION OF DEPOSIT REQUIREMENTS

I, Ellen J. Kapinos, declare as follows:

1. That I am an attorney of record and Senior Patent Attorney of Genetics Institute, the assignee of the above-identified patent application;
2. That the cultures listed below have been deposited in the permanent culture collection of the American Type Culture Collection, 12031 Parklawn Drive, Rockville, Maryland, and the culture deposits meet the requirements of the Budapest Treaty for the purposes of patent procedure;
3. That said cultures have been accorded the accession numbers 75010 and 75011, prior to the filing date of the above-identified patent application;
4. That said cultures have been deposited under conditions which ensure that access thereto will be available during the pendency of the above-identified patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 AND 35 U.S.C. 122;
5. That upon issuance of a patent on the above-identified patent application Genetics Institute, Inc. will remove any restrictions as to public availability of the culture deposits, and

will replace the same culture deposits should they become nonviable, during the period that extends thirty years from the date of the deposit, or the period of the enforceable life of the patent, or the period of five years after the last public request for the deposit, whichever period is longest; and

6. That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief and believed to true, and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 10 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Genetics Institute, Inc.

Date: August 3, 1993

By: Ellen J. Kapinos
Ellen J. Kapinos
Senior Patent Attorney

PATENT

Serial No. 800,111 Doc. No. 574-9-05 Atty/Sec Ex/INN Date Aug 4, 1993
Inventor David M. Dick, Jack Wang, John W. Zaney, Tony Colaste
Title Lipase and Collagen Inductase Enzymes

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

| | | | | | | | |
|-------------------------------------|--|--------|----------|-------------------------------------|----------------------------|------------------------|---------------------|
| <input type="checkbox"/> | pp. Spec., | Claim, | Abstract | <input checked="" type="checkbox"/> | 20 | pp. Amendment: OA dtd | <u>Z-5-93</u> |
| <input type="checkbox"/> | pp. Declaration/Power of Attorney | | | <input type="checkbox"/> | 1 | pp. Response: OA dtd | |
| <input type="checkbox"/> | pp. Verified Statement (Small Entity) | | | <input type="checkbox"/> | 1 | pp. Transmittal Letter | <u>in Duplicate</u> |
| <input type="checkbox"/> | shts. Informal Drawings | | | <input type="checkbox"/> | Issue Fee | | |
| <input type="checkbox"/> | shts. Formal Drawings | | | <input type="checkbox"/> | Notice of Appeal & Fee | | |
| <input type="checkbox"/> | pp. Assignment | | | <input type="checkbox"/> | Check # | for \$ | |
| <input type="checkbox"/> | pp. Preliminary Amendment | | | <input checked="" type="checkbox"/> | <u>Deposit Declaration</u> | | |
| <input checked="" type="checkbox"/> | pp. Extension of Time <u>induplicate</u> | | | <input type="checkbox"/> | <u>PCT / US 91 / 03388</u> | | |
| <input checked="" type="checkbox"/> | pp. Information Disclosure Statement | | | <input type="checkbox"/> | | | |
| | with PTO-1499 and 10 references | | | | | | |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

VIA Express Mail
RC 72J 966 8844US

Respectfully,
Genetics Institute, Inc.

PATENT

Serial No. 800,111 Doc. No. 574-9-05 Atty/Sec Ex/INN Date Aug 4, 1993
Inventor David M. Dick, Jack Wang, John W. Zaney, Tony Colaste

Title Lipase and Collagen Inductase Enzymes

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

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|-------------------------------------|--|--------|----------|-------------------------------------|----------------------------|------------------------|---------------------|
| <input type="checkbox"/> | pp. Spec., | Claim, | Abstract | <input checked="" type="checkbox"/> | 20 | pp. Amendment: OA dtd | <u>Z-5-93</u> |
| <input type="checkbox"/> | pp. Declaration/Power of Attorney | | | <input type="checkbox"/> | 1 | pp. Response: OA dtd | |
| <input type="checkbox"/> | pp. Verified Statement (Small Entity) | | | <input type="checkbox"/> | 1 | pp. Transmittal Letter | <u>in Duplicate</u> |
| <input type="checkbox"/> | shts. Informal Drawings | | | <input type="checkbox"/> | Issue Fee | | |
| <input type="checkbox"/> | shts. Formal Drawings | | | <input type="checkbox"/> | Notice of Appeal & Fee | | |
| <input type="checkbox"/> | pp. Assignment | | | <input type="checkbox"/> | Check # | for \$ | |
| <input type="checkbox"/> | pp. Preliminary Amendment | | | <input checked="" type="checkbox"/> | <u>Deposit Declaration</u> | | |
| <input checked="" type="checkbox"/> | pp. Extension of Time <u>induplicate</u> | | | <input type="checkbox"/> | <u>PCT / US 91 / 03388</u> | | |
| <input checked="" type="checkbox"/> | pp. Information Disclosure Statement | | | <input type="checkbox"/> | | | |
| | with PTO-1499 and 10 references | | | | | | |



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

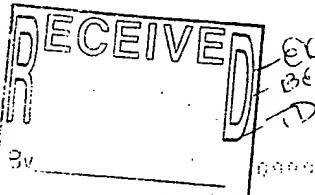
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER FILING DATE FIRST NAMED APPLICANT ATTY DOCKET NO./TITLE

07/800,364 11/26/91 HEMICK

71225

LEGAL AFFAIRS DEPARTMENT
GENETICS INSTITUTE INC. 87
CAMBRIDGE MA 02149



DATE MAILED:

**NOTICE TO FILE MISSING PARTS OF APPLICATION
FILING DATE GRANTED**

A filing date has been granted to this application. However, the following parts are missing

If all missing parts are filed within the period set below, the total amount owed by applicant as a

large entity, small entity (verified statement filed), is \$ 130

1. The statutory basic filing fee is: missing insufficient. Applicant as a large entity small entity, must submit \$ _____ to complete the basic filing fee and MUST ALSO SUBMIT THE SURCHARGE AS INDICATED BELOW.

2. Additional claim fees of \$ _____ as a large entity small entity, including any required multiple dependent claim fees, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due. NO SURCHARGE IS REQUIRED FOR THIS ITEM.

The oath or declaration:

- is missing.
- does not cover items omitted at time of execution.

An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED.

4. The oath or declaration does not identify the application to which it applies. An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.

5. The signature to the oath or declaration is: missing; a reproduction; by a person other than the inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW..

6. The signature of the following joint inventor(s) is missing from the oath or declaration:

_____. An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Receipt Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.

- 7. The application was filed in a language other than English. Applicant must file a verified English translation of the application and a fee of \$30.00 under 37 CFR 1.17(k), unless this fee has already been paid. NO SURCHARGE IS REQUIRED FOR THIS ITEM.
- 8. A \$50.00 processing fee is required for returned checks. (37 CFR 1.21(m)).
- 9. Your filing receipt was mailed in error because check was returned without payment.
- 10. Other.

An App

identified above in items 1 and 3-6 must be timely provided ALONG WITH THE PAYMENT OF A SURCHARGE of \$120.00 for large entities or \$60.00 for small entities who have filed a verified statement claiming such status. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given ONE MONTH FROM THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE of this application, WHICHEVER IS LATER, within which to file all missing parts and pay any fees required above to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

Direct the response to, and any questions about, this notice to ATTENTION: Application Division, Special Handling Unit.

A copy of this notice MUST be returned with response.

For: Manager, Application Division

Manager, NPP
(703) 557-1233

360

GI 5182A

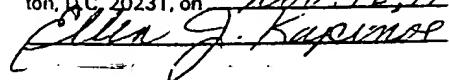
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Hewick et al.) GROUP ART UNIT: 1814
SERIAL NO.: 07/800,364) EXAMINER: K. FURMAN
FILED : 26 November 1991)
TITLE : Bone and Cartilage Inductive Proteins)

BOX SEQUENCE
Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

November 11, 1992

I hereby certify that this correspondence is being
deposited with the United States Postal Service
in an envelope addressed to
Commissioner of Patents and Trademarks, Wash-
ington, D.C. 20231, on November 12, 1992.

PETITION AND FEE FOR EXTENSION OF TIME UNDER 37 CFR 1.136

We hereby request an extension of time for response of two (2) month/s pursuant to 37 CFR 1.136(a) in which to respond to the Notice to Comply with Requirements for Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. This extension resets the time for response from September 12, 1992 to November 12, 1992.

We authorize the charging of \$360.00 and any additional fees and crediting of overpayment to our Deposit Account 07-1060, and for this purpose, we enclose a duplicate copy of this petition.

Respectfully submitted,

Date: November 12, 1992


Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicant
87 Cambridge Park Drive
Cambridge, MA 02140
(617) 876-1170

GI 5182A
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Hewick, et al
Application Serial No. : 07/800,364
Filing Date : 26 November 1991
For : Bone and Cartilage Inductive Proteins

November 11, 1992

Box Sequence
Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

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deposited with the United States Postal Service
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Commissioner of Patents and Trademarks, Wash-
ton, D.C. 20231, on Nov. 12, 1992

STATEMENT PURSUANT TO 37 CFR 1.825(a)

Sir:

Pursuant to the attached notice dated August 12, 1992 received from the Patent and Trademark Office that the "Sequence Listing" does not comply with the requirements of §§ 1.821 through 1.825 because Sequence to human BMP-8 in Fig. 2 does not comply with the sequence rules, applicant herewith submits an amended Sequence Listing and Preliminary Amendment.

Please substitute this amended Sequence Listing for the originally-filed Sequence Listing. The Sequence Listing and enclosed diskette contain amendments to SEQ ID NOS 1-12 to correct defects and now contains SEQ ID NOS. 1-14.

In addition, the Application Serial Number and filing date are now available and have been provided in the appropriate location in the Sequence Listing.

These amendments present no substantive changes to the Sequences as originally filed. No new matter has been added.

Respectfully submitted,

Date: Nov. 12, 1992

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicant

87 Cambridge Park Drive
Cambridge, MA 02140

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Hewick et al) GROUP ART UNIT: 1814
SERIAL NO.: 07/800,364)
FILED : 26 November 1991)
TITLE : BONE AND CARTILAGE)
INDUCTIVE PROTEINS)

November 11, 1992

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

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as first class mail in an envelope addressed to
Commissioner of Patents and Trademarks, Washi-
ton, D.C. 20231, on November 12, 1992

Ellen J. Furman

PRELIMINARY AMENDMENT

Sir:

In response to the Notice to Comply with Sequence Requirements
mailed August 12 and in accordance with the sequence requirements
of 37 CFR 1.821(d) please amend the application as follows:

In the Specification:

Insert --(SEQ ID NO: 14)-- after "Figure 2" on the following
pages:

page 1, line 34
page 4, line 5

Insert --(SEQ ID NO: 13)-- after "Figure 2" on the following
pages:

page 3, line 1
page 6, line 24

Insert --(SEQ ID NOS: 13 and 14)-- after "Figure 2" on the
following pages:

page 7, line 15
page 35, line 30

HEWICK ET AL
November 11, 1992
Page - 2 -

In the Claims:

Insert --(SEQ ID NO: 14)-- after "Figure 2" in the following claims:

Claims 1(e), 4, 5, 12, 19, and 25

Insert --(SEQ ID NO: 13)-- after "Figure 2" in the following claims:

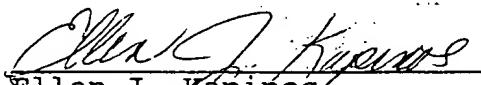
Claims 6 (d) and (e), 7 and 8

REMARKS

Reference to Sequence ID numbers has been made in the specification and claims. The sequences of Figure 2 are depicted (as now referenced in the specification and claims) in SEQ ID NOS: 13 and 14. It is believed that this amendment addresses paragraph 5 of the Notice to Comply. Paragraph 5 indicates that a sequence of the "Listing" is not properly referenced. Though BMP-8 was not originally in the "Listing" it is understood that this is the sequence intended in paragraph 5.

Respectfully submitted,

Date: Nov. 12, 1992


Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicant/s

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Hewick et al) GROUP ART UNIT: 1814
SERIAL NO.: 07/800,364) EXAMINER: K. Furman
FILED : 26 November 1991)
TITLE : BONE AND CARTILAGE)
INDUCTIVE PROTEINS)

November 11, 1992

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

I hereby certify that this correspondence is being
deposited with the United States Postal Service
first class mail in an envelope addressed to
Commissioner of Patents and Trademarks, Washi-
ton, D.C. 20231, on Nov. 12, 1992

STATEMENT PURSUANT TO 37 CFR 1.821(f)

Sir:

Pursuant to the duty to submit DNA and amino acid sequence in computer readable form, this affirms that to the best of my knowledge and belief, the content of the SEQUENCE LISTING as provided after the specification and before the claims in the above-identified patent application and the computer readable copy of said SEQUENCE LISTING provided herewith are the same.

Respectfully submitted,

Date: Nov. 12, 1992

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicant

87 CambridgePark Drive
Cambridge, MA 02140
(617) 876-1170

(1) GENERAL INFORMATION:

(i) APPLICANT: Hewick, Rodney M.
Wang, Jack H.
Wozney, John M.
Celeste, Anthony J.

(ii) TITLE OF INVENTION: Bone and Cartilage Inductive Proteins

(iii) NUMBER OF SEQUENCES: 14

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Legal Affairs, Genetics Institute, Inc.
(B) STREET: 87 CambridgePark Drive
(C) CITY: Cambridge
(D) STATE: MA
(E) COUNTRY: USA
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/800,364
(B) FILING DATE: 26-NOV-1991
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Kapinos, Ellen J.
(B) REGISTRATION NUMBER: 32,245
(C) REFERENCE/DOCKET NUMBER: GI 5182A

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617-876-1170
(B) TELEFAX: 617-876-5851

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp
 1 5 10 15
 Val Ile Ala Pro Gln Gly Tyr
 20

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile
 1 5 10 15

Leu Arg

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ala Cys Cys Ala Pro Thr Lys
 1 5

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Asn | Glu | Leu | Pro | Pro | Pro | Asn | Lys | Leu | Pro | Gly | Ile | Phe | Asp | Asp |
| 1 | | | | 5 | | | | | | 10 | | | | | 15 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|--|--|--|--|
| Val | His | Gly | Ser | His | Gly | Arg | | | | | | | | | |
| | | | | 20 | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 80 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus

(vii) IMMEDIATE SOURCE:

- (B) CLONE: acc30

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 25..57

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

| | | | | | | | | | | | | | | | |
|------------|------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|
| GGATCCGCGT | GCTGTGCTCC | GACC | AAG | CTG | AGC | GCC | ACC | TCC | GTG | CTC | TAC | | | | |
| 1 | | | | | | | | | | | | | | | |
| | Lys | Leu | Ser | Ala | Thr | Ser | Val | Leu | Tyr | | | | | | |
| | | | | | 5 | | | | | | | | | | |

TAC GAC AGCAGCAACA ATGTAATTCT AGA
Tyr Asp
10

44

80

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp
1 5 10

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 199 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Bos Taurus

(vii) IMMEDIATE SOURCE:
(A) LIBRARY: Bovine genomic
(B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:
(C) UNITS: bp

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 30..199

(ix) FEATURE:
(A) NAME/KEY: intron
(B) LOCATION: 1..29

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 30..179

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TGCCCGCTGC CCCCTCCCGC CCCCCGCCAG GTG CAC CTG CTG AAG CCG CAC GCG
Val His Leu Leu Lys Pro His Ala
1 5

53

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 49 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear
- ii) MOLECULE TYPE: protein
- xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| Val | His | Leu | Leu | Lys | Pro | His | Ala | Val | Pro | Lys | Ala | Cys | Cys | Ala | Pro | 1 | 5 | 10 | 15 |
| Thr | Lys | Leu | Ser | Ala | Thr | Ser | Val | Leu | Tyr | Tyr | Asp | Ser | Ser | Asn | Asn | 20 | 25 | 30 | |
| Val | Ile | Leu | Arg | Lys | His | Arg | Asn | Met | Val | Val | Arg | Ala | Cys | Gly | Cys | 35 | 40 | 45 | |
| His | | | | | | | | | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 172 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: *Bos taurus*
- (vii) IMMEDIATE SOURCE:
 - (A) LIBRARY: Bovine genomic
 - (B) CLONE: Lambda 9800-10
- (viii) POSITION IN GENOME:
 - (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 51..161

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..50

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 162..172

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 51..161

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

| | |
|---|----|
| GGGGTGGGAG GGCACGTGGA TGGGACTCAC CTTCTCCCAC TACCCCCCAG GAC TGG | 56 |
| Asp Trp | |
| 1 | |
| GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC | |
| Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys | |
| 5 10 15 | |
| TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG | |
| Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu | |
| 20 25 30 | |
| CAG TCC CTG GTCAGTACCT C | |
| Gln Ser Leu | |
| 35 | |

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

| | |
|---|--|
| Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly | |
| 1 5 10 15 | |
| Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala | |
| 20 25 30 | |
| Ile Leu Gln Ser Leu | |
| 35 | |

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 119 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Bovine genome
- (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 20..99

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..19

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 100..119

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 22..99

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CCCTTGCCTG TCCCCGAGA C GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG
 Asp Val His Gly Ser His Gly Arg Gln Val
 1 5 10

51

TGC CGT CGG CAC GAG CTG TAC GTG AGC TTC CAG GAC CTG GGC TGG CTG
 Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu
 15 20 25

99

GTGAGTTCCG ACTCTCCTTT

119

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

48

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Val | His | Gly | Ser | His | Gly | Arg | Gln | Val | Cys | Arg | Arg | His | Glu | Leu |
| 1 | | | | 5 | | | 10 | | | 15 | | | | | |
| Tyr | Val | Ser | Phe | Gln | Asp | Leu | Gly | Trp | Leu | | | | | | |
| | | | 20 | | | | 25 | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1003 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
- (F) TISSUE TYPE: Human Heart

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Human heart cDNA library stratagene catalog
#936208
- (B) CLONE: hH38

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 8..850

(ix) FEATURE:

- (A) NAME/KEY: mat_peptide
- (B) LOCATION: 427..843

(ix) FEATURE:

- (A) NAME/KEY: mRNA
- (B) LOCATION: 1..997

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

| | | |
|--|------|------|
| GAATTCC GAG CCC CAT TGG AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile | 49 | |
| -139 | -135 | -130 |

| | | | |
|--|------|------|------|
| CCG GCT GGG GAG GCG GTC ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val | 97 | | |
| -125 | -120 | -115 | -110 |

| | | |
|--|------|-----|
| CCC AGC ATC CAC CTG CTC AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG Pro Ser Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln | 145 | |
| -105 | -100 | -95 |

| | | |
|--|-----|-----|
| GTG GTC CAG GAG CAG TCC AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT Val Val Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp | 193 | |
| -90 | -85 | -80 |

| | |
|---|-----|
| CTT CAG ACG CTC CGA GCT GGA GAC GAG GGC TGG CTG GTG CTG GAT GTC Leu Gln Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val -75 -70 -65 | 241 |
| ACA GCA GCC AGT GAC TGC TGG TTG CTG AAG CGT CAC AAG GAC CTG GGA Thr Ala Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly -60 -55 -50 | 289 |
| CTC CGC CTC TAT GTG GAG ACT GAG GAT GGG CAC AGC GTG GAT CCT GGC Leu Arg Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly -45 -40 -35 -30 | 337 |
| CTG GCC GGC CTG CTG GGT CAA CGG GCC CCA CGC TCC CAA CAG CCT TTC Leu Ala Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe -25 -20 -15 | 385 |
| GTG GTC ACT TTC TTC AGG GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG Val Val Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg -10 -5 1 | 433 |
| GCA GTG AGG CCA CTG AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG Ala Val Arg Pro Leu Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu 5 10 15 | 481 |
| CCG CAG GCC AAC CGA CTC CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC Pro Gln Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser 20 25 30 35 | 529 |
| CAC GGC CGG CAG GTC TGC CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG His Gly Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln 40 45 50 | 577 |
| GAC CTT GGC TGG CTG GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala 55 60 65 | 625 |
| TAT TAC TGT GAG GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn 70 75 80 | 673 |
| GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG GTG CAC CTG ATG AAG CCA Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro 85 90 95 | 721 |
| AAC GCA GTC CCC AAG GCG TGC TGT GCA CCC ACC AAG CTG AGC GCC ACC Asn Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr 100 105 110 115 | 769 |
| TCT GTG CTC TAC TAT GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His 120 125 130 | 817 |
| CGC AAC ATG GTG GTC AAG GCC TGC GGC TGC CAC TGAGTCAGCC CGCCCCAGCCC Arg Asn Met Val Val Lys Ala Cys Gly Cys His 135 140 | 870 |
| TACTGCAGCC ACCCTTCTCA TCTGGATCGG GCCCTGCAGA GGCAGAAAAC CCTTAAATGC TGTACAGCT CAAGCAGGAG TGTCAGGGGC CCTCACTCTC GGTGCCTACT TCCTGTCAGG | 930 |
| | 990 |

CTTCTGGAA TTC

1003

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 281 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala
 -139 -135 -130 -125

Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser
 -120 -115 -110

Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val
 -105 -100 -95

Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln
 -90 -85 -80

Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val Thr Ala
 -75 -70 -65 -60

Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly Leu Arg
 -55 -50 -45

Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly Leu Ala
 -40 -35 -30

Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe Val Val
 -25 -20 -15

Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg Ala Val
 -10 -5 1 5

Arg Pro Leu Arg Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln
 10 15 20

Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly
 25 30 35

Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu
 40 45 50

Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr
 55 60 65

Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr
 70 75 80 85

Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro Asn Ala
 90 95 100

Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val
105 110 115

Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn
120 125 130

Met Val Val Lys Ala Cys Gly Cys His
135 140

PATENTSerial No. 800,364 Doc. No. 5182A Atty/Sec. EK/AIN Date NOV. 12, 1992Inventor RON HENICK ET AL.Title Bone and Cartilage Endocrine Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

pp. Spec., Claim, Abstract pp. Amendment: OA dtd 8/12/92
 pp. Declaration/Power of Attorney pp. Response: OA dtd _____
 pp. Verified Statement (Small Entity) pp. Transmittal Letter
 shts. Informal Drawings Issue Fee
 shts. Formal Drawings Notice of Appeal & Fee
 pp. Assignment Check # _____ for \$ _____
 pp. Preliminary Amendment Statement Pursuant to 37 CFR 1.82(a)
 pp. Extension of Time & Fee Sequence Listing pp 41-51
 pp. Information Disclosure Statement Copy of Notice to Comply to
with PTO-1499 and _____ references Sequence Disclosure
 Statement Pursuant to 37 CFR

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Respectfully,
Genetics Institute, Inc.

1-821(F)

PATENTSerial No. 800,364 Doc. No. 5182A Atty/Sec. EK/AIN Date NOV. 12, 1992Inventor RON HENICK ET AL.Title Bone and Cartilage Endocrine Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

pp. Spec., Claim, Abstract pp. Amendment: OA dtd 8/12/92
 pp. Declaration/Power of Attorney pp. Response: OA dtd _____
 pp. Verified Statement (Small Entity) pp. Transmittal Letter
 shts. Informal Drawings Issue Fee
 shts. Formal Drawings Notice of Appeal & Fee
 pp. Assignment Check # _____ for \$ _____
 pp. Preliminary Amendment Statement Pursuant to 37 CFR 1.82(a)
 pp. Extension of Time Sequence Listing pp 41-51
 pp. Information Disclosure Statement Copy of Notice to Comply to
with PTO-1499 and _____ references Sequence Disclosure
 Statement Pursuant to 37 CFR

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1-821(F)



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| | | | |
|---------------|-------------|----------------------|---------------------|
| SERIAL NUMBER | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
| 07/800, 364 | 11/26/91 | HEWICK | R 5182A |
| | | EXAMINER | |

LEGAL AFFAIRS DEPT.
GENETICS INSTITUTE, INC.
87 CAMBRIDGE PARK DR.
CAMBRIDGE, MA 02140

RECEIVED 2/8/93
5/5/93 86-1983

| | |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
| 3814 | 10 |

DATE MAILED: 02/05/93
5/5/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined Responsive to communication filed on 1-4-93 This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892. 2. Notice re Patent Drawing, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449. 4. Notice of Informal Patent Application, Form PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474. 6.

Part II SUMMARY OF ACTION

1. Claims 1-25 are pending in the application.

Of the above, claims 1-5, 10-12 and 20-25 are withdrawn from consideration.

2. Claims _____ have been cancelled.

3. Claims _____ are allowed.

4. Claims 6-9 and 13-19 are rejected.

5. Claims _____ are objected to.

6. Claims _____ are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable. not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been approved by the examiner. disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed on _____, has been approved. disapproved (see explanation).

12. Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has been received not been received
 been filed in parent application, serial no. _____; filed on _____

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other

EXAMINER'S ACTION

Serial No. 07/800,364
Art Unit 1814

15. Restriction to one of the following inventions is required under 35

U.S.C. § 121:

5 I. Claims 1-5, 10-12 and 20-25, drawn to BMP-8 proteins, pharmaceuticals and methods of treatment, classified in Class 514, subclass 12; and Class 530, subclass 350.

10 II. Claims 6-9 and 13-19, drawn to DNAs, host cells and methods of producing recombinant BMP-8, classified in Class 536, subclass 27; Class 435, subclass 240.2+, depending upon the nature of the cell, and subclass 69.1.

15 16. The inventions are distinct, each from the other because of the following reasons:

The inventions of Group II and Group I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the protein can be made by purification from natural sources using convention purification techniques or combinations of purification techniques including, ion exchange chromatography, hydrophobic interaction chromatography, thiophilic adsorption chromatography, immunoaffinity purification techniques, ultrafiltration, density gradient ultracentrifugation, reverse-phase HPLC and/or other conventional purification techniques. Additionally, the DNA and products containing the DNA of Group II are chemically distinct compounds having separate status in the art as show by their diverse classification and the DNA and host cells can be used other than to make the protein, such as to make additional DNA for use as a probe to detect and/or obtain the same or similar nucleic acid molecules.

35 17. If Group I is elected, Claims 1, 2, 10 and 20-24 are generic to a plurality of disclosed patentably distinct species comprising (1) species a) of claim 1; (2) species b) of claim 1; (3) species c) of claim 1; (4) species

d) of claim 1; (5) species e) of claim 1 (i.e. the mature protein also in claims 4, 12 and 25); (6) the species of claim 5, i.e. the intact protein plus presequence) and (7) the human BMP of ATCC #75010 (claims 3 and 11). These species are distinct one from the other because they are drawn to different 5 amino acid sequences required and/or proteins of different size which include portions of sequence not included in the other species which requires searching not required for the other species and therefore requires a separate field of search though they may be classified together. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this 10 requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the 15 examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

18. If Group II is elected, Claims 6, 13 and 17 are generic to a plurality 20 of disclosed patentably distinct species comprising (1) species a) of claim 6; (2) species b) of claim 6; (3) species c) of claim 6; (4) species d) of claim 6 encoding the intact protein plus presequence (also in claims 7, 14 and 19); (5) species e) of claim 6 (i.e. encoding the mature protein also in claims 8 and 15); (6) the DNA of ATCC #75010 including introns (claims 9, 16 and 18). 25 These species are distinct one from the other because they are drawn to different DNA sequences required and/or DNAs of different size which include portions of sequence not included in the other species which requires searching not required for the other species. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement 30 is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

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examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

5 19. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and because the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

10 20. During a telephone conversation with Ellen Kapinos on 1-15-93 a provisional election was made with traverse to prosecute the invention of Group II, claim 6-9 and 13-19 and the species of (4) above which reads upon 6, 7, 14 and 19. However, since no prior art was found for the elected species, all the species were searched and examined on the merits in Group II.

15 Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-5, 10-12 and 20-25 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

20 21. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

25 22. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

30 23. The following is a quotation of the first paragraph of 35 U.S.C. § 112: The specification shall contain a written description of the invention,

5

and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10

24. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention. The written description is inadequate because the amino acid sequence of bovine BMP-8 is stated in the last line of p. 32 as corresponding to that of SEQ ID NO: 13. However, this is incorrect for two reasons: (1) SEQ ID NO:13 is a nucleic acid sequence (even though the amino acid sequence is shown); and (2) both SEQ ID NO:13 and SEQ ID NO: 14 correspond to the human BMP-8 nucleic acid and amino acid sequences, respectively, not the bovine amino acid sequence shown in Table 4. Since none of the SEQ ID numbers of the specification correspond to the bovine BMP-8 amino acid sequence of Table 4 and since the bovine amino acid sequence differs from the human sequence at only three amino acid positions, it is suggested that the specification refer to the bovine BMP-8 amino acid sequence of Table 4 as corresponding to the sequence of SEQ ID NO: 14 from amino acid position number 31 through position 142 wherein Met at position 97 is replaced with Leu, Asn at position 100 is replaced with His and Lys at position 137 is replaced with Arg.

15

The written description is also inadequate because numerous other references to SEQ ID numbers are confusing. At numerous places in the specification particular amino acid or nucleic acid position numbers of a Figure are referred and a particular SEQ ID NO: in parenthesis immediately follows the reference to the Figure but it is not clear whether the sequence of the SEQ ID NO: is the equivalent of the entire sequence of the Figure or the equivalent of the sequence corresponding to the range of positions in the Figure. For example, see line 34 of p. 2 (which is not numbered as page 2) through line 1 of p. 3 and lines 4 and 5 of p. 4. Additionally, the position numbers of the Figure do not correspond to the numbers of the SEQ ID NO:.

Therefore, if applicant refers to both the Figure or Table and the SEQ ID NO: the positions should be specifically noted for each where the sequence is less than the full sequence of the SEQ ID NO.

5 25. Claims 6, 13 and 17 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to where the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2. See M.P.E.P. §§ 706.03(n) and 706.03(z). The scope of the claims must bear a reasonable 10 correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The scope of the claims is not reasonably correlated with the scope of enablement of the instant specification because the claims are directed to DNAs which encode a BMP-8 protein, which proteins are defined in the specification as having the ability to stimulate, promote or otherwise induce 15 bone and/or cartilage formation (see p. 3, lines 2-4 and line 24 of p. 4 through p. 6 of the specification), but are limited to merely comprising one of sequences a), b) or c) of the Markush grouping of claim 6. The DNAs of species a), b) and c) of claim 6 have not been shown to encode by themselves (i.e., absent the other coding regions of that set forth in sequence e) of 20 claim 6), to encode a BMP-8 protein having the activities described and would not be expected, by themselves, to encode peptides having this activity since they lack substantial portions of the mature protein. The DNAs comprising at least one of species a), b) and c) are not limited to encoding a protein of particular size which occurs naturally in the source it was obtained from and 25 are open to include any possible addition DNA sequence at either end. However, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the 30 protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge

of the ways in which the proteins' structure relates to its function. However, the knowledge that may be gleaned from the known members of the BMP family of proteins is limited and precise regions critical to activity do not appear to have been known. Further, it would clearly require undue 5 experimentation to determine the extremely broad scope encompassed by the claims of other non-homologous amino acid sequences which nevertheless have sufficient tertiary structure similarity or other structural similarities sufficient to impart BMP-8 activity to use for the parts of the BMP-8 protein which are not encoded by each of species a), b) or c).

10 While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result 15 of such modifications representative of the essentially infinite the scope broadly set forth is unpredictable based on the instant disclosure and the prior art. Further, one skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Additionally, the 20 specification fails to provide guidance with regard to (A) the general tolerance to modification and extent of such tolerance; (B) specific positions and regions of the sequence(s) which can be predictably modified; (C) which regions are critical to activity; (D) what fragments, if any, can be made which retain the biological activity of the intact protein; and (E) the 25 specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See 30 Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546

(Bd. Pat. App. & Int. 1986).

In addition to the scope set forth above by the Examiner as being reasonably correlated with the enablement of the specification, some additional or other modifications which could be made and used with a reasonable expectation of success, or which would otherwise not require undue experimentation, would also be obvious (e.g. DNAs encoding BMP-8 proteins with minor conservative amino acid substitutions). The specification, however, does not appear to provide antecedent basis for the language of limitations which would encompass all such obvious modifications either because such obvious modifications are not specifically defined or classed in the instant specification, or because it cannot be readily determined or succinctly stated which modifications are so obvious. Therefore, it is expressly noted for the record by the Examiner that limiting the scope of the claims so as to be included within the scope set forth above by the Examiner as enabled should not preclude applicant(s) from protecting under the doctrine of equivalents such additional or other modifications which would also be obvious.

26. Claims 17 and 18 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited wherein the protein recovered in step (b) is the one encoded by the coding regions of the DNA sequence of in step (a) in both claims 17 and 18, and in claims 17 wherein the sequence is either that set forth in d) or e) or DNAs which encode the same protein(s) encoded by the DNAs of species d) of e). See M.P.E.P. §§ 706.03(n) and 706.03(z). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). However, the instant claim does not bear a reasonable correlation with the scope of the enablement because step (b) broadly includes the recovery of any protein having the functional limitations of the ability to induce cartilage and/or bone formation which may be in addition to or even instead of the protein produced by the DNA set forth in step (a). However, applicants have not enabled the extremely broad scope representative of all proteins having

this function which may even include many other proteins structurally unrelated to the BMP family of proteins nor representative of all possible modifications of the proteins of the BMP family since the amino acid sequence of a given protein determines its structure/function and the sequence

5 information contained in the sequences of the proteins of the BMP family is limited and because it is not routine in the art to screen for multiple substitutions (i.e. beyond that which can be reasonably deduced from differences between homologous proteins having the same structure) to obtain functionally equivalent molecules. Thus, undue experimentation would be
10 required to support the broad scope of step (b) of the claim. Claim 17 should be limited to the DNA of species d) or e) of as set forth in claim 6 or DNAs which encode the same protein(s) encoded by the DNAs of species d) or e) for the reasons discussed above in the immediately preceding rejection under 35 U.S.C. § 112, first paragraph, regarding the scope of claims 6, 13 and 17.

15 27. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the claimed invention. It is apparent that ATCC #75010 set forth in claim 9 and referred to on p. 34 of the instant specification is required to practice the claimed invention because
20 the precise sequence of the DNA encoding BMP-8 of ATCC #75010 is not elsewhere disclosed and this DNA is specifically claimed in claims 9 and 18. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of ATCC #75010. See 37
25 C.F.R. 1.802.

The specification does not provide a repeatable method for obtaining ATCC #75010 and it does not appear to be readily available material. Deposit of ATCC #75010 would satisfy the enablement requirements of 35 U.S.C. § 112.
30 If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who

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is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty (as already set forth on p. 34 of the instant specification) and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements.

5 See 37 C.F.R. 1.808.

10 28. Claims 9 and 18 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

15 29. Claims 6-8, 13-15 and 19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6-8 and 19 are indefinite because particular amino acid or nucleic acid position numbers of a Figure are referred and a particular SEQ ID NO: in parenthesis immediately follows the reference to the Figure but it is not 20 clear whether the sequence of the SEQ ID NO: is the equivalent of the entire sequence of the Figure or the equivalent of the sequence corresponding to the range of positions in the Figure. See species d) and e) of claim 6 and claims 6-8. Additionally, the position numbers of the Figure do not correspond to the numbers of the SEQ ID NO:. Therefore, if applicant refers to both the 25 Figure or Table and the SEQ ID NO: the positions should be specifically noted for each where the sequence is less than the full sequence of the SEQ ID NO. However, to avoid redundancy it is suggested that the claims refer only to the SEQ ID NO: and any specific positions thereof rather than to the Figures.

30 30. Claim 19 is objected to because step (a) contains no reference to a SEQ ID NO: which is required (see 37 CFR § 1.821(d)).

31. 35 U.S.C. § 101 reads as follows:

5 Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

32. Claims 6, 9, 13 and 16 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The DNAs of 10 species a), b) and c) of claim 6 and of claim 9 and the host cells, as claimed, has the same characteristics and utility as that found in nature. To overcome this rejection the Examiner suggests the amendment of the claims to include purity limitations which would distinguish the characteristics and utility of applicant's DNA as enabled in the specification from the utility of 15 the DNA it exists in nature. The DNAs of claims 6 and 9 are not limited to having been isolated and the open-ended term "comprising" in claim 6 leaves the claim open to include the other naturally occurring sequence and 20 ingredients associated with these DNAs. The species of claim 9 includes the naturally occurring introns and is not limited to having been isolated. With respect to the host cells of claims 13 and 16, regardless of whether the 25 claims are amended to wherein the DNA is isolated, a host cell merely limited to being transformed with such isolated DNA, would still encompass the natural cells containing the genes since product-by-process limitations would not distinguish over the same products occurring naturally. It is noted that the other products of the claims are not included in the instant rejection because 30 the DNAs are limited with respect to purity and/or inherently exclude naturally occurring intron regions. For relevant case law see Farbenfabriken of Elberfeld Co. v. Kuehmsted, 171 Fed. 887, 890 (N.D. Ill. 1909) (text of claim at 889); Parke-Davis & Co. v. H.D. Mulford Co., 189 Fed. 95, 103, 106, 965 (S.D.N.Y. 1911) (claim 1); and In re Bergstrom, 427 F.2d 1394, 1398, 1401-1402 (CCPA 1970).

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33. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The reference of Oppermann et al discloses similar osteogenic proteins and some DNA sequences thereof with their amino acid sequences aligned along with other homologous proteins having somewhat 5 different function/utility (see Figure 18).

34. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 10 1814.

35. Papers relating to this application may be submitted to Group 1810 by facsimile transmission. Papers should be faxed to Group 1810 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-15 4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

36. Any inquiry concerning this communication or earlier communications from 20 the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

25 January 28, 1993

Keith C. Furman
KEITH C. FURMAN, Ph.D.
PATENT EXAMINER
ART UNIT 1814

30

10

602 366

GROUP 18/14

NOTICE OF DRAFTSMAN'S PATENT DRAWING REVIEW

The PTO Draftsmen review all originally filed drawings regardless of whether they were designated as informal or formal.

The drawings filed 1/15/61/92

A. are approved.

B. are objected to under 37 CFR 1.84 for reason(s) checked below. The examiner will require submission of new, corrected drawings at the appropriate time. Corrected drawings must be submitted according to the instructions listed on the back of this Notice.

1. Paper and Ink. 37 CFR 1.84(a)

Poor Quality Paper. Must Be White.
Transparent Paper Not Allowed.

Sheet(s) _____

2. Size of Sheet and Margins. 37 CFR 1.84(b)

Acceptable Paper Sizes and Margins

Paper Size

| Margin | 8 1/2 by 14 inches | 8 1/2 by 13 inches | DIN size A4 21 by 29.7 cm. |
|--------|--------------------|--------------------|-------------------------------|
| Top | 2 inches | 1 inch | 2.5 cm. |
| Left | 1/4 inch | 1/4 inch | 2.5 cm. |
| Right | 1/4 inch | 1/4 inch | 1.5 cm. |
| Bottom | 1/4 inch | 1/4 inch | 1.0 cm. |

Proper Size Paper Required. All Sheets Must be Same Size.

Sheet(s) _____

Proper Margins Required.

Sheet(s) _____

Top Right
 Left Bottom

3. Character of Lines. 37 CFR 1.84(c)

Lines Pale, Rough and Blurred, or Jagged. Fig(s) _____

Solid Black Shading Not Allowed. Fig(s) _____

Photographs Not Approved.

 Comments:

5. Hatching and Shading. 37 CFR 1.84(d)

Shade Lines are Required. Fig(s) _____

Criss-Cross Hatching Not Allowed. Fig(s) _____

Double Line Hatching Not Allowed. Fig(s) _____

Parts in Section Must be Hatched Properly. Fig(s) _____

6. Reference Characters. 37 CFR 1.84(f)

Reference Characters Poor or Rough and Blurred. Fig(s) _____

Minimum 1/8 inch (3.2 mm.) in height is required. Fig(s) _____

Figure Legends Poor or Placed Incorrectly. Fig(s) _____

7. Views. 37 CFR 1.84(i) & (j)

Figures Must be Numbered Separately.

Figures Must Not be Connected Fig(s) _____

8. Identification of Drawings. 37 CFR 1.84(l)

Extraneous Matter or Copy Machine Marks Not Allowed. Fig(s) _____

Changes Not Completed from Prior PTO-948 dated _____

Telephone inquiries concerning this review should be directed to the Chief Draftsman at telephone number (703) 557-6404.

2/20/92

Reviewing Draftsman

Date

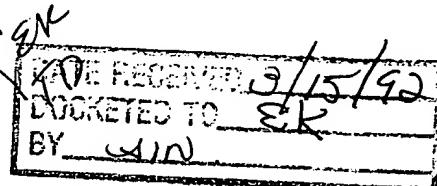
FILING RECEIPT


 UNITED STATES DEPARTMENT OF COMMERCE
 Patent and Trademark Office
 ASSISTANT SECRETARY AND COMMISSIONER
 OF PATENTS AND TRADEMARKS
 Washington, D.C. 20231

20

| SERIAL NUMBER | FILING DATE | GRP ART UNIT | FIL FEE REC'D | ATTORNEY DOCKET NO. | DRWGS | TOT CL | IND CL |
|---------------|-------------|--------------|---------------|---------------------|-------|--------|--------|
| 07/800,364 | 11/26/91 | 1806 | \$1,460.00 | 5182A | 3 | 25 | 13 |

LEGAL AFFAIRS DEPT.
 GENETICS INSTITUTE, INC.
 87 CAMBRIDGE PARK DR.
 CAMBRIDGE, MA 02140



Receipt is acknowledged of the patent application identified herein. It will be considered in its order and you will be notified as to the examination thereof. Be sure to give the U.S. SERIAL NUMBER, DATE OF FILING, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this transmittal.

Applicant(s) RODNEY M. HEWICK, LEXINGTON, MA; JACK H. WANG, LEXINGTON, MA; JOHN M. WOZNEY, HUDSON, MA; ANTHONY J. CELESTE, HUDSON, MA.

CONTINUING DATA AS CLAIMED BY APPLICANT-
 THIS APPLN IS A CIP OF 07/525,357 05/16/90
 AND A CIP OF 07/641,204 01/15/91

FOREIGN/PCT APPLICATIONS-PCT

PCT/US91/03388 05/15/91

FOREIGN FILING LICENSE GRANTED 02/19/92
 TITLE
 BONE AND CARTILAGE INDUCTIVE PROTEINS

PRELIMINARY CLASS: 514

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rodney M. Hewick et al

Serial No.: 07/800,364

Filed : November 26, 1991

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 24, 1992

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

RESPONSE TO NOTICE TO FILE MISSING PARTS
OF APPLICATION UNDER 37 C.F.R. 1.53(d)

Sir:

In response to a Notice to File Missing Parts of Application under 37 C.F.R. Section 1.53(d) issued in connection with the above-identified application on January 6, 1992, Applicants hereby submit their Declaration and Power of Attorney pursuant to 37 C.F.R. Section 1.63.

The Declaration refers to the application's above-identified serial number and filing date. As indicated in the Notice, the deadline for submitting the Declaration is February 6, 1992.

Authorization is hereby given to charge the \$120 (One-hundred twenty dollar) surcharge under 37 C.F.R. Section 1.16(e) and any additional fees which may be required in this regard, and to credit any overpayment to Deposit Account No. 07-1060. Two duplicate copies of this letter are enclosed.

Respectfully submitted,

Ellen J. Kapinos
Ellen J. Kapinos
Registration No. 32,245
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140-2387
Phone (617) 876-1170
Fax (617) 876-5851

I hereby certify that this correspondence is being deposited with the United States Postal Service in first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992.

Ellen J. Kapinos

I hereby certify that this correspondence is being
mailed with the United States Postal Service as
first class mail in an envelope addressed to Com-
missioner of Patents and Trademarks, Washing-
ton, D.C. 20231, on July 24, 1992

Docket No. GI 5182

See my briefs
Declaration and Power of Attorney

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am ~~the original, first and sole inventor (if only one name is listed below) or~~ an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

BONE AND CARTILAGE INDUCTIVE PROTEINS

the specification of which: _____ is attached hereto.

X was filed on 11/26/91 as

Application Serial No. 07/800,364

and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information of which I am aware which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

| <u>Number</u> | <u>Country</u> | <u>Day/Month/Year Filed</u> | <u>Priority Claimed Yes/No</u> |
|----------------|----------------|-----------------------------|------------------------------------|
| PCT/US91/03388 | designated: | 15 May 1991 | Yes |

I hereby claim the benefit under Title 35, United States Code, section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

| <u>Application Serial No.</u> | <u>Filing Date</u> | <u>Status</u> |
|-------------------------------|--------------------|---------------|
| 07/525,357 | 16 May 1990 | Pending |
| 07/641,204 | 15 January 1991 | Pending |

*Austria, Belgium, Switzerland and Liechtenstein, Germany, France, United Kingdom, Italy, Luxembourg, Netherlands, Sweden, Denmark, Spain, Greece, Japan, and Canada

I hereby appoint the following attorneys to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith, to file any International Applications which are based thereon under the provisions of the Patent Cooperation Treaty and to act on my behalf before the competent International Authorities: Bruce M. Eisen, Reg. No. 22,847; Thomas J. DesRosier, Reg. No. 30,168; Luann Cserr, Reg. No. 31,822; Ellen J. Kapnos, Reg. No. 32,245; and Patricia McDaniels, Reg. No. 33,194.

Address all correspondence to **Legal Affairs Department, Genetics Institute, Inc., 87 Cambridge Park Drive, Cambridge, MA 02140**. Telephone number: 617-876-1170.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Rodney M. Hewick

Inventor's signature R. M. Hewick

Citizenship GB Date: 1/24/92 Residence: 16 Woodcliffe Road
Lexington, MA 02173
USA

Post Office address (if different) _____

Full name of second joint inventor: Jack H. Wang

Inventor's signature J. H. Wang

Citizenship US Date: 1/24/92 Residence: 522 Lowell Street
Lexington, MA 02173
USA

Post Office address (if different) _____

Full name of third joint inventor: John M. Wozney

Inventor's signature John M. Wozney

Citizenship US Date: 1/24/92 Residence: 59 Old Bolton Road
Hudson, MA 01749
USA

Post office address (if different) _____

Full name of fourth joint inventor Anthony J. Celeste

Inventor's signature Anthony J. Celeste

Citizenship US

Date 1/24/92

Residence 86 Packard St., Hudson, MA 01749 USA

Post Office Address (if different) _____

Full name of fifth joint inventor _____

Inventor's signature _____

Citizenship _____

Date _____

Residence _____

Post Office Address (if different) _____

Full name of sixth joint inventor _____

Inventor's signature _____

Citizenship _____

Date _____

Residence _____

Post Office Address (if different) _____

PATENT

Serial No. 07/800,364 Doc. No. 5182A Atty/Sec ER/EZ Date 1/24/92
Inventor Rudney M. Hewick et al
Title Bone + Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon

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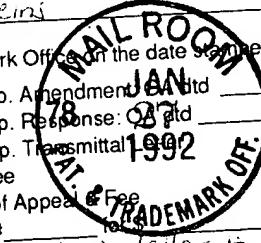
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PATENT

Serial No. 07/800,364 Doc. No. 5182A Atty/Sec ER/EZ Date 1/24/92
Inventor Rudney M. Hewick et al
Title Bone + Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon

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| <input checked="" type="checkbox"/> 3 pp. Spec., <input type="checkbox"/> Claim, <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Amendment, <input type="checkbox"/> dtd |
| <input type="checkbox"/> pp. Declaration/Power of Attorney | <input type="checkbox"/> pp. Response, <input type="checkbox"/> old |
| <input type="checkbox"/> pp. Verified Statement (Small Entity) | <input type="checkbox"/> pp. Transmittal, <input type="checkbox"/> 1992 |
| <input type="checkbox"/> shs. Informal Drawings | <input type="checkbox"/> Issue Fee |
| <input type="checkbox"/> shs. Formal Drawings | <input type="checkbox"/> Notice of Appeal, <input type="checkbox"/> Fee |
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| <input type="checkbox"/> pp. Extension of Time | <input type="checkbox"/> Impacted |
| <input type="checkbox"/> pp. Information Disclosure Statement with PTO-1499 and <input type="checkbox"/> references | <input checked="" type="checkbox"/> Copy of Notice to the Missing Parts |



The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Respectfully,
Genetics Institute, Inc.

Send U.S. First Class mail



B
19-

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rodney M. Hewick et al
Serial No.: 07/800,364
Filed : November 26, 1991
For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 24, 1992

Hon. Commissioner of Patents
and Trademarks
Box Assignment
Washington, DC 20231



LETTER

SIR:

Enclosed is an assignment of the above-identified application, executed January 24, 1992, to Genetics Institute, Inc., a corporation of Delaware.

Authorization is hereby given to charge the \$8.00 recordation fee and any additional fees which may be required in this regard, and to credit any overpayment, to Deposit Account No. 07-1060. Two duplicate copies of this letter are enclosed.

Respectfully submitted,


Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617) 876-1170

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992.



115988 FRAME 717

US14256 02/03/92 07800364

07-1060 140 581

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UNITED STATES DEPARTMENT OF COMMERCE

Patent and Trademark Office

ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

5182A

DATE: 02/25/92

TO:

ELLEN J. KAPINOS
GENETICS INSTITUTE, INC.
87 CAMBRIDGE PARK DRIVE
CAMBRIDGE, MA 02140

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS, ON THIS NOTICE, PLEASE SEND A REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR:

HEWICK, RODNEY M.

DOC DATE: 01/24/91

ASSIGNOR:

WANG, JACK H.

DOC DATE: 01/24/91

ASSIGNOR:

WOZNEY, JOHN M.

DOC DATE: 01/24/91

ASSIGNOR:

CELESTE, ANTHONY J.

DOC DATE: 01/24/91

RECORDATION DATE: 01/27/92 NUMBER OF PAGES 003 REEL/FRAME 5988/0717

DIGEST :ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:

GENETICS INSTITUTE, INC.
A CORPORATION OF DE
87 CAMBRIDGE PARK DRIVE
CAMBRIDGE, MASSACHUSETTS

SERIAL NUMBER 7-800364 FILING DATE 11/26/91
PATENT NUMBER ←
ISSUE DATE 10/00/00

22

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992

See m. B. j. h.s.

GI 5182A
USSN 07/800,364
Filing Date 11/26/91
Group Art Unit

ASSIGNMENT

In consideration of good and valuable considerations, the receipt of which is hereby acknowledged, we, the undersigned, Rodney M. Hewick, Jack H. Wang, John M. Wozney, and Anthony Celeste residing at:

16 Woodcliffe Road, Lexington, MA 02173
522 Lowell Street, Lexington, MA 02173

59 Old Bolton Road, Hudson, MA 01749
86 Packard Street, Hudson, MA 01749 respectively
hereby sell, assign and transfer to Genetics Institute, Inc. a corporation of the State of Delaware having a place of business at 87 CambridgePark Drive, Cambridge, in the County of Middlesex and the State of Massachusetts, its successors, assigns and legal representatives, the entire right, title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned on and is entitled

BONE AND CARTILAGE INDUCTIVE PROTEINS

(GI case no. 5182A) and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for United States Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorize and request the Commissioner of Patents of the United States to issue to said Assignee, the corporation above named, its successors, assigns and legal representatives, in accordance with this assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;

Agree that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and may sue for and recover profits and damages for any and all infringements thereof; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known

1115988 FMM718

GI 5182A USSN 07/800,364 Filing Date 11/26/91
Group Art Unit _____

and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives;

Authorize my/our attorney to insert hereon * the serial number, filing date and group art unit of the United States patent application referred to above after the same shall have been made known to such attorney by the United States Patent Office; and

Covenant with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.

Rodney M. Hewick

[L.S.]

Rodney M. Hewick

Jack H. Wang

[L.S.]

Jack H. Wang

John M. Wozney

[L.S.]

John M. Wozney

Anthony J. Celeste

[L.S.]

Anthony J. Celeste

Commonwealth of Massachusetts

Middlesex County S.S. Date 1/24/91

then personally appeared the above named

Rodney M. Hewick, Jack H. Wang, John M. Wozney, Anthony J. Celeste

and acknowledged the foregoing instrument to be his/her free act and deed before me

Ellen M. Zaglakas, NOTARY PUBLIC.

My commission expires on February 18, 1994

Signed Ellen M. Zaglakas

RECORDED
PATENT AND TRADEMARK
OFFICE
JAN 27 1992

*Insertion of the serial number, filing date and group art unit of the application referred to above was made by me this 24th day of January, 1992.

Ellen J. Kapinos
Attorney for Applicant(s)

Ellen J. Kapinos

Reg. No. 32,245

REF 5988 FILED 7/19



GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rodney M. Hewick et al
Serial No.: 07/800,364
Filed : November 26, 1991
For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 24, 1992

Hon. Commissioner of Patents
and Trademarks
Box Assignment
Washington, DC 20231



RECEIVED
SEARCH & EXAMINER

20231-4 NM:21

LETTER

SIR:

Enclosed is an assignment of the above-identified application, executed January 24, 1992, to Genetics Institute, Inc., a corporation of Delaware.

Authorization is hereby given to charge the \$8.00 recordation fee and any additional fees which may be required in this regard, and to credit any overpayment, to Deposit Account No. 07-1060. Two duplicate copies of this letter are enclosed.

Respectfully submitted,

Ellen J. Kapinos
Ellen J. Kapinos
Reg. No. 32,245
Attorney for Applicants
(617) 876-1170

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992.

Ellen J. Kapinos

US14256 02/03/92 07800364

07-1060 140 581

40.00CH

1015988 1044717

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992

Dear Mr. Bejekos

GI 5182A
USSN 07/800,364
Filing Date 11/26/91
Group Art Unit

ASSIGNMENT

In consideration of good and valuable considerations, the receipt of which is hereby acknowledged, we, the undersigned, Rodney M. Hewick, Jack H. Wang, John M. Wozney, and Anthony Celeste residing at:

16 Woodcliffe Road, Lexington, MA 02173
522 Lowell Street, Lexington, MA 02173
59 Old Bolton Road, Hudson, MA 01749
86 Packard Street, Hudson, MA 01749 respectively hereby sell, assign and transfer to Genetics Institute, Inc. a corporation of the State of Delaware having a place of business at 87 CambridgePark Drive, Cambridge, in the County of Middlesex and the State of Massachusetts, its successors, assigns and legal representatives, the entire right, title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned on and is entitled

BONE AND CARTILAGE INDUCTIVE PROTEINS

(GI case no. 5182A) and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for United States Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorize and request the Commissioner of Patents of the United States to issue to said Assignee, the corporation above named, its successors, assigns and legal representatives, in accordance with this assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;

Agree that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and may sue for and recover profits and damages for any and all infringements thereof; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known

11718 889553

GI 5182A . . . USSN 07/800,364 Filing Date 11/26/91
Group Art Unit _____

and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives;

Authorize my/our attorney to insert hereon * the serial number, filing date and group art unit of the United States patent application referred to above after the same shall have been made known to such attorney by the United States Patent Office; and

Covenant with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.

Rodney M. Hewick

[L.S.]

Rodney M. Hewick

Jack H. Wang

[L.S.]

Jack H. Wang

John M. Wozney

[L.S.]

John M. Wozney

Anthony J. Celeste

[L.S.]

Anthony J. Celeste

Commonwealth of Massachusetts

Middlesex County S.S. Date 1/24/91

then personally appeared the above named

Rodney M. Hewick, Jack H. Wang, John M. Wozney, Anthony J. Celeste
and acknowledged the foregoing instrument to be his/her free act and deed before me

Ellen M. Zaglakas, NOTARY PUBLIC.

My commission expires on February 18, 1994

Signed Ellen M. Zaglakas

RECORDED
PATENT AND TRADEMARK
OFFICE
JAN 27 1992

*Insertion of the serial number, filing date and group art unit of the application referred to above was made by me this 24th day of January, 1992.

Ellen J. Kapinos
Attorney for Applicant(s)

Ellen J. Kapinos

Reg. No. 32,245

598844719



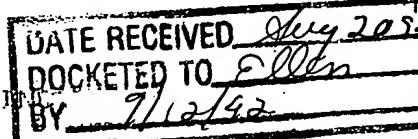
UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

18

| SERIAL NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|---------------|-------------|-----------------------|---------------------|
| 800,364 | 11/26/91 | HEWICK | R 5102A |

LEGAL AFFAIRS DEPT.
GENETICS INSTITUTE,
87 CAMBRIDGE PARK DR.
CAMBRIDGE, MA 02140



| EXAMINER | |
|--------------|--------------|
| FURMAN, K | |
| ART UNIT | PAPER NUMBER |
| 1814 | |
| DATE MAILED: | |

08/12/92

9/12/92

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 CFR 1.821 through 1.825 for one or more of the reasons set forth on the attached form "Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/Or Amino Acid Sequence Disclosures," wherein attention is directed to paragraphs 4d and 5.

Any inquiry concerning this communication should be directed to Examiner Keith Furman, Art Unit 1814, whose telephone number is (703) 308-3453.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS
CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE
DISCLOSURES

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 CFR §§ 1.821 through 1.825 as follows:

1. This application clearly fails to comply with the collective requirements of §§ 1.821 through 1.825. Applicant's attention is directed to these regulations, a copy of which is attached.

2. This application does not conform exclusively to the requirements of §§ 1.821 through 1.825. The non-conforming material should be deleted. § 1.821(b).

3. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing." § 1.821(c).

4. This application does contain, as a separate part of the disclosure on paper copy, a "Sequence Listing." However, the "Sequence Listing" does not comply with the requirements of §§ 1.821 through 1.825 as follows:

a. The sequence data does not comply with the symbol and format requirements of paragraphs (b) through (p) of § 1.822. Specifically: _____

b. The "Sequence Listing" does not comply with the location and page requirements of paragraph (a) of § 1.823.

c. The "Sequence Listing" does not comply with the information requirements of paragraph (b) of § 1.823. Specifically: _____

d. Other: Sequences to human BMPs in Figure 2 do not comply with the sequence rules

5. The description and/or claims of the patent application mention a sequence that is set forth in the "Sequence Listing" but reference is not properly made to the sequence by use of a sequence identifier as required by § 1.821(d).

6. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by § 1.821(e).

7. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the computer readable form does not comply with the requirements of § 1.824. Specifically: _____

8. A statement that the content of the paper and computer readable copies are the same has not been submitted as required by § 1.821(f).

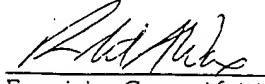
9. The amendment to or replacement of the paper and/or computer readable copies of the "Sequence Listing" does not comply with the requirements of § 1.825(a) through (c).

10. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable. Applicant must provide a substitute copy of the data in computer readable form accompanied by a statement that the substitute data is identical to that originally filed. § 1.825(d). Specifically: _____

11. Other: _____

APPLICANT IS GIVEN ONE MONTH FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE ABOVE REQUIREMENTS. Failure to comply with the above requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136. Direct the response to, and any questions about, this notice to the undersigned. A copy of this notice MUST be returned with your response.

For: Manager, Application Processing Division
(703) 308-1202 or 308-_____


Examining Group 18/4
(703) 308-4216



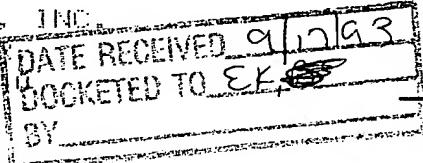
UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

(14)

| SERIAL NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|---------------|-------------|-----------------------|---------------------|
| 077800, 364 | 11/26/91 | HEWLETT | R 5162A |

LEGAL AFFAIRS DEPT.
GENETICS INSTITUTE, INC.
87 CAMBRIDGE PARK DR.
CAMBRIDGE, MA 02142



| EXAMINER | |
|-------------|--------------|
| FRANCIS, E. | |
| ART UNIT | PAPER NUMBER |
| | 11 |

DATE MAILED: 9/14/93

NOTICE OF ABANDONMENT

This application is abandoned in view of:

- Applicant's failure to respond to the Office letter, mailed 2-5-93.
- Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
- Applicant's failure to timely file the response received _____ within the period set in the Office letter.
- Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of _____ of the Notice of Allowance.

The issue fee was received on _____.

The issue fee has not been received in Allowed Files Branch as of _____.

In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.

- Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
- The corrected and/or substitute drawings were received on _____.

- The reason(s) below.

Keith R. Larson
KEITH R. LARSON
PATENT EXAMINER
GROUP 1800

| | | | | | | | | |
|---|--------------|---------|--|------|-----------------------|----------------|-------------------------------------|--------------|
| FORM PTO-892 (REV. 2-92) | | | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | | SERIAL NO. | GROUP/ART UNIT | ATTACHMENT TO PAPER NUMBER | 10 |
| NOTICE OF REFERENCES CITED | | | APPLICANT(S) | | <i>Hewrich et al.</i> | | | |
| U.S. PATENT DOCUMENTS | | | | | | | | |
| * | DOCUMENT NO. | DATE | NAME | | CLASS | SUB-CLASS | FILING DATE IF APPROPRIATE | |
| A | 5011691 | 4-30-91 | <i>Oyzenmann et al.</i> | | 424 | 423 | | |
| B | | | | | | | | |
| C | | | | | | | | |
| D | | | | | | | | |
| E | | | | | | | | |
| F | | | | | | | | |
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| K | | | | | | | | |
| FOREIGN PATENT DOCUMENTS | | | | | | | | |
| * | DOCUMENT NO. | DATE | COUNTRY | NAME | CLASS | SUB-CLASS | PERTINENT SHTS. DWG | PP. SPEC. |
| L | | | | | | | | |
| M | | | | | | | | |
| N | | | | | | | | |
| O | | | | | | | | |
| P | | | | | | | | |
| Q | | | | | | | | |
| OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.) | | | | | | | | |
| R | | | | | | | | |
| S | | | | | | | | |
| T | | | | | | | | |
| U | | | | | | | | |
| EXAMINER | DATE | | | | | | | |
| <i>Walt Fisner</i> | 1-28-93 | | | | | | | |
| * A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).) | | | | | | | | |

PATENT Date Oct 5, 1994
Serial No. 07/800,364 Doc. No. GI 5182A Atty/Sec. EK/DG

Inventor Hewick et al
Title DNA Encoding and Methods For Producing BMP-8 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

on Spec. pp. Sequence ID Listing/Computer Diskette 15 pp. Amendment/Response
Abstract 15 pp. Preliminary Amendment
iter Diskette(s) 15 pp. Amendment/Response
string 825(a) 15 pp. Declaration/Exhibits
ney 825(b) 15 pp. Transmittal Letter (triplicate)
, P. PTO 948 15 pp. Appeal Brief (triplicate)
Issue Fee
aplicate) 2pp Notice of Appeal & Fee 16pp Appendix
ment & Fee 2pp Drawing Transmittal
ices

s respectfully requested to place its stamp on this postal card

Respectfully,
Genetics Institute, Inc.

3967900 US

PATENT Date Oct 5, 1994
Serial No. 07/800,364 Doc. No. GI 5182A Atty/Sec. EK/DG
Inventor Hewick et al
Title DNA Encoding and Methods For Producing BMP-8 Proteins

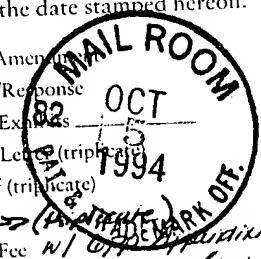
The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

on Spec. claims (1-), Abstract pp. Preliminary Amendment
 13 pp. Sequence ID Listing/Computer Diskette 15 pp. Amendment/Response
 12 pp. Statement re Sequence ID Listing 825(a) 15 pp. Declaration/Exhibits
 15 pp. Declaration/Power of Attorney 15 pp. Transmittal Letter (triplicate)
 13 shts. Informal/Formal Drawings 16. PTO 948 15 pp. Appeal Brief (triplicate)
 15 pp. Assignment & Fee 15 pp. Issue Fee
 11 pp. Extension of Time & Fee (duplicate) 2pp Notice of Appeal & Fee 16pp Appendix
 15 pp. Information Disclosure Statement & Fee 2pp Drawing Transmittal (duplicate)
with PTO-1449 and references

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card
and place it in the outgoing mail.

Respectfully,
Genetics Institute, Inc.

Express Mail Label No. RB 793967900 US



| | | | |
|----------------------------------|--|--------------------------------|-----------------------|
| Form PTO-1449 | | Atty. Docket No. GI 5182A | Serial No. 07/800,364 |
| INFORMATION DISCLOSURE STATEMENT | | Applicant(s) Rod Hewick et al. | |
| | | Filing Date November 26, 1991 | Group 1814 |

U.S. PATENT DOCUMENTS

| Examiner Initial | | Document Number | Date | Name | Class | Subclass | Filing Date (If Appropriate) |
|------------------|----|-----------------|----------|--------------------------|-------|----------|------------------------------|
| | AA | 4,804,744 | 2/14/89 | Sen | 530 | 350 | |
| | AB | 4,774,228 | 9/27/88 | Seyedin | 514 | 21 | |
| | AC | 4,774,322 | 9/27/88 | Seyedin | 530 | 353 | |
| | AD | 4,434,094 | 2/28/84 | Seyedin and Thomas | 530 | 416 | |
| | AE | 4,627,982 | 12/9/86 | Seyedin and Thomas | 424 | 95 | |
| | AF | 4,563,350 | 1/7/86 | Nathan | 424 | 95 | |
| | AG | 4,294,753 | 10/31/81 | Urist | 530 | 395 | |
| | AH | 4,455,256 | 6/19/84 | Urist | 530 | 350 | |
| | AI | 4,968,590 | 11/6/90 | Kuberasampath and Rueger | 530 | 326 | |
| | AJ | 4,761,471 | 8/2/88 | Urist | 530 | 350 | |

FOREIGN PATENT DOCUMENTS

| Examiner Initial | | Document Number | Date | Country | Class | Subclass | Translation Yes/No |
|------------------|-----|-----------------|----------|-----------------------|-------|----------|--------------------|
| | BA | 4 165 78A2 | 5/9/90 | European Patent Appn. | C12N | 15/00 | |
| | BB | 4 094 72 A1 | 11/7/90 | European Patent Appn. | C12N | 15/12 | |
| | BC | 33 6760 | 6/4/89 | European Patent Appn. | C07K | 7/00 | |
| | BD | 2 017466 | 5/24/90 | Canada | C12N | 15/16 | |
| | *BE | WO 91/18047 | 11/28/91 | WIPO | | | |

OTHER DOCUMENTS (Including Author, Title, Pertinent Pages, etc.)

| | | |
|--|-----|---|
| | CA | Urist et al., <u>Science</u> , 220: 680-686 (1983) |
| | CB | Luyten et al., <u>The Journal of Biological Chemistry</u> , 264(23) 13377-13380 (August 15, 1989) |
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